COVER PAGE

Official Title:	A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia
NCT number:	NCT02255435
Document Date:	21 April 2025

RTA 408

408-C-1402

US IND NUMBER: 122349

EU CT NUMBER: 2024-517436-22

A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

VERSION 14.0 – 21 APRIL, 2025

The information contained herein is confidential and the proprietary property of Reata Pharmaceuticals, Inc., and any unauthorized use or disclosure of such information without the prior written authorization of Reata Pharmaceuticals, Inc. is expressly prohibited.

SPONSOR APPROVAL AND SIGNATURE PAGE

[redacted], PharmD
[redacted]
Biogen

Date (*DD MMM YYYY*)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for RTA 408. I have read the 408-C-1402 clinical study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc., a wholly owned subsidiary of Biogen

Name of Investigational Products:
RTA 408 Capsules

Name of Active Ingredient:
RTA 408

Title of Study:
A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia

EU CT Number:
2024-517436-22

Study center(s): Up to approximately 20 study centers

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled in Part 1: November 2014 Estimated date last patient completed Part 2: December 2018 Extended access until the drug is available through commercial channels or alternate post-trial access mechanisms	2

Objectives:

In patients with Friedreich's ataxia, comparing those receiving RTA 408 versus those receiving the placebo, the objectives are as follows:

Part 1:

Primary:

- To evaluate the change in peak work during maximal exercise testing
- To evaluate the safety and tolerability of RTA 408

Secondary:

- To evaluate the change in the modified Friedreich's ataxia rating scale (mFARS) score

Exploratory:

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in performance on a 25-foot timed walk test
- To evaluate the change in performance on a low-contrast letter visual acuity test
- To evaluate the change in performance on a 9-hole peg test (9-HPT)
- To evaluate the change in Fatigue Severity Scale score
- To evaluate the change in SF-36® Health Survey Update (SF-36) score
- To evaluate the change in the full neurological Friedreich's ataxia rating scale (FARS) score

- [redacted]
- [redacted]
- To evaluate the change in pharmacodynamic (PD) markers of activity in platelet, [redacted]
- To characterize the pharmacokinetics (PK) of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules

Part 2:

Primary:

- To evaluate the change in the mFARS score at Week 48
- To evaluate the safety and tolerability of RTA 408

Secondary:

- To evaluate the change in peak work during maximal exercise testing at Week 48
- To evaluate the Patient Global Impression of Change at Week 48
- To evaluate the Clinical Global Impression of Change at Week 48

Exploratory:

- To evaluate the distribution of change in mFARS scores at Week 48
- To evaluate the change in SF-36 score
- To evaluate the change in performance on a 9-HPT
- To evaluate the change in performance on a 25-foot timed walk test
- To evaluate the change in the Activities of Daily Living (ADL) score
- To evaluate the frequency of falls
- To characterize the PK of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules

Extension:

- To provide continuing open-label treatment with RTA 408 while collecting ongoing safety and tolerability data with RTA 408

Methodology:

This study will evaluate the efficacy, safety, and PD of RTA 408 in the treatment of patients with Friedreich's ataxia.

Part 1: The first part of the study will be a randomized, placebo-controlled, double-blind, dose-ranging study to evaluate the safety, efficacy, and PD activity of RTA 408 at 2.5 mg, 5 mg, 10 mg, 20 mg, and higher dose levels (not to exceed 300 mg) in patients with Friedreich's ataxia. A cohort consists of the next eight eligible patients randomized 3:1 to RTA 408 at the cohort specific dose (n=6) or placebo (n=2). Up to approximately 9 cohorts will be enrolled in Part 1 to allow for adequate dose-ranging for selection of a dose of RTA 408 to be used in Part 2.

Intra-patient dose-escalation will only be utilized in the first cohort to evaluate RTA 408 at the first two dose levels (2.5 mg and 5 mg). Patients enrolling in the first cohort will be randomized to

RTA 408 2.5 mg or placebo. After the Week 2 visit, each patient in the first cohort will dose-escalate to 5 mg (or remain on placebo) on Day 15 unless a dose-limiting toxicity (DLT) is reported in that patient (Section 7.4.3). After the last patient in the first cohort completes their Week 4 visit (i.e., 2 weeks on 2.5 mg daily [or matching placebo] followed by 2 weeks on 5 mg daily [or matching placebo]), the data safety monitoring board (DSMB) and Sponsor will review all available safety information and make a decision regarding enrollment of the next cohort.

Beginning with the second 8-patient cohort, once the eighth patient enrolled completes their Week 2 visit the DSMB will review all available safety information and recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is 300 mg. The dose level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data. Prior to opening each cohort in Part 1 for enrollment, the Sponsor will also evaluate all available data from doses studied in Part 1 to determine if enough information is available to select doses for Part 2 of the study. Once enrollment begins in Part 2, no additional cohorts will be enrolled in Part 1.

If the Sponsor or DSMB considers dose escalation not safe for any reason, no more dose escalation will be carried out. The DSMB may recommend stopping dose escalation at any time, particularly if their review of adverse events (AEs) or laboratory data (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase [ALP], magnesium, creatinine, B-type natriuretic peptide [BNP], etc.), reveals any potential safety concern. The Sponsor, in addition to reviewing all available safety and efficacy data, will also take into consideration the predicted systemic exposure to RTA 408 at the next proposed dose in comparison with the exposure vs adverse effect profile for RTA 408 in animals. If systemic exposure is sufficiently high to warrant a potential concern based on animal toxicity data, dose escalation may be stopped or paused, if needed, to seek additional input from the DSMB or the United States Food and Drug Administration (US FDA).

Part 2: The second part of this study will be a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of RTA 408 150 mg in patients with Friedreich's ataxia. Patients enrolled in Part 2 will be randomized 1:1 to receive RTA 408 150 mg, or placebo. Randomization will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will not comprise more than 20% of patients enrolled in Part 2. The RTA 408 dose of 150 mg was selected for Part 2 based on DSMB and Sponsor review of available data from Part 1, including safety, efficacy, PK, and PD data. Following randomization on Day 1, patients will self-administer study treatment once daily for 48 weeks. A follow-up visit for safety will occur at Week 52 (4 weeks after the last dose). The DSMB will perform quarterly reviews of unblinded data for safety throughout Part 2.

Extension: The extension will assess long-term safety and tolerability of RTA 408 in qualified patients with Friedreich's ataxia following completion of Part 1 or Part 2. Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study.

Patients will receive open-label RTA 408 (150 mg) once daily until the drug is available through commercial channels or alternate post-trial access mechanisms, or until patient withdrawal, whichever is sooner. All patients in the extension will follow the same visit and assessment schedule. Extension Day 1 is defined as the first day treatment is dispensed to the patient for the extension, following completion of Part 1 or Part 2. All other extension visits will be relative to extension Day 1. Patients will be scheduled for in-person assessments during treatment in the extension at Day 1, Week 4, Week 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Day 14.

Since Part 2 patients will be followed continuously within the study, eligibility for the extension should be assessed at the Week 52 visit and a separate screening visit is not required. After confirming eligibility for Part 2 patients, study treatment for extension Day 1 should be dispensed following the Week 52 assessments. Part 1 patients will not have been followed continuously within this study, and therefore must complete a screening visit to confirm eligibility.

The conduct of the extension phase, according to protocol specifications, was impacted by the Coronavirus Disease 2019 (COVID-19) pandemic. As a result, and as of Version 10 of the protocol, modifications intended to address access to and administration of investigational product, and adherence to protocol-specified visits and laboratory assessments was implemented. These modifications are described in Appendix 13 (COVID-19 Mitigations).

Number of patients (planned):

Up to approximately 172 patients will be enrolled in this study (up to 72 patients in Part 1 and approximately 100 patients in Part 2).

The extension will only include qualified patients from Part 1 and Part 2.

Inclusion criteria (Part 1 and Part 2):

Patients must:

1. Have genetically confirmed Friedreich's ataxia
2. Have an mFARS score ≥ 20 and ≤ 80. The average of the two mFARS values collected at Screening and Day 1 visits must fall within the allowable range, and they must be within 4.5 points of each other
3. Be male or female and ≥ 16 years of age and ≤ 40 years of age
4. Have no changes to their exercise regimen within 30 days prior to Study Day 1 and be willing to remain on the same exercise regimen during the study period
5. Have the ability to complete maximal exercise testing
6. Have adequate kidney function defined as an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula
7. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
8. Be able to swallow capsules
9. Be willing and able to cooperate with all aspects of the protocol
10. Be willing to practice medically acceptable methods of birth control (Section 9.7.2)
11. Provide written informed consent for study participation, approved by the appropriate Institutional Review Board (IRB)

Exclusion criteria (Part 1 and Part 2):

Patients must not:

1. Have uncontrolled diabetes (HbA1c > 11.0%)
2. Have BNP level > 200 pg/mL
3. Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease

   b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
   c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
   d. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
   e. History of hospitalization for heart failure in the last five years
   f. Cardiac insufficiency, defined as New York Heart Association Class > 2
   g. History of atrial fibrillation
   h. History of unstable arrhythmias
4. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (B or C)
5. Have known or suspected active drug or alcohol abuse, as per investigator judgment
6. Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal (ULN) of AST or ALT. Levels above this threshold are allowable if attributable to muscle injury
7. Have any abnormal laboratory test value or clinically significant pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by study enrollment
8. Have taken any of the following drugs within 7 days prior to Study Day 1 or plan to take any of these drugs during the time of study participation:
   a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
   b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)
   c. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
9. Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, at screening, clinically relevant deviations in laboratory tests including any one of the following:
   a. ALT and/or AST > 1.5-fold ULN
   b. bilirubin > 1.2-fold ULN
   c. ALP > 2-fold ULN
   d. albumin < lower limit of normal (LLN)
10. Have participated in any other interventional clinical study within 30 days prior to Study Day 1
11. Have a cognitive impairment that may preclude ability to comply with study procedures
12. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator
13. Have used antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and vitamin E above the recommended daily allowance, within 14 days prior to Study Day 1, or plan to take any of these supplements during the time of study participation
14. Have previously documented mitochondrial respiratory chain disease
15. Have a history of thromboembolic events within the past 5 years
16. Have taken anticoagulant therapy within 30 days prior to Study Day 1
17. Have scheduled surgical treatment for scoliosis or foot deformity during the study

18. Have had significant suicidal ideation within 1 month prior to Screening Visit as per investigator judgment or any history of suicide attempts
19. Be pregnant or breastfeeding
20. Prior participation in a trial with RTA 408

Extension eligibility:

Patients must complete 12 weeks of treatment in Part 1 or 48 weeks of treatment in Part 2, have no major protocol deviations, and continue to meet inclusion and exclusion criteria as specified in Appendix 1.

Investigational product, dosage and mode of administration:

RTA 408 Capsules (2.5 mg, 10 mg, or 50 mg) will be administered orally.

Duration of treatment:

Part 1: RTA 408 or placebo administered orally once daily for 12 weeks;

Part 2: RTA 408 or placebo administered orally once daily for 48 weeks;

Extension: RTA 408 administered orally once daily and with extended access until the drug is available through commercial channels or alternate post-trial access mechanisms, or until patient withdrawal, whichever is sooner.

Reference therapy, dosage, and mode of administration:

Matching placebo capsules will be administered orally (Part 1 and Part 2 only).

Criteria for evaluation:

Efficacy (Part 1): Parameters collected during maximal exercise testing (including peak work), FARS test (including mFARS score), 25-foot walk timed test, low-contrast letter visual acuity test, 9-HPT, Fatigue Severity Scale, SF-36, [redacted]

Efficacy (Part 2): FARS test (including mFARS score); parameters collected during maximal exercise testing (including peak work), 9-HPT, 25-foot timed walk test, ADL, SF-36, Patient Global Impression of Change, Clinical Global Impression of Change, and fall diary

Safety (Part 1 and Part 2): Results of echocardiogram, electrocardiogram (ECG), vital sign measurements, weight, body mass index (BMI), physical examinations, AEs, serious AEs (SAEs), concomitant medications, and laboratory test results (clinical chemistry, hematology, urinalysis, microscopy, and pregnancy tests [as indicated])

Safety (Extension): Vital sign measurements, physical examination results, AEs, SAEs, weight, and assessment of BNP and N-terminal prohormone of B-type natriuretic protein (NT-proBNP).

Pharmacokinetic (Part 1 and Part 2): RTA 408 plasma concentration data

Pharmacodynamic (Part 1): Parameters assessed from [redacted] platelet, and [redacted] samples.

Extension: Results of physical examinations, laboratory results, vital sign measurements, weight, AEs, SAEs, concomitant medications, pregnancy tests (as indicated), FARS, ADL, 9-HPT, 25-foot timed walk test.

Statistical methods:

Sample size:

The sample size for Part 1 is based on a dose-escalation scheme to evaluate initial safety and PD activity of RTA 408 in this patient population. The small number of patients at each dose in Part 1 is

not expected to fully characterize safety, efficacy, or PD, but rather inform the DSMB and Sponsor of the appropriate doses to select for Part 2.

With 100 patients, the Part 2 portion of the study will have over 80% power to test the difference between the two treatment groups with respect to change from baseline in mFARS at Week 48. The power calculation, which was based on a 2-sided t-test, assumes the following:

- Two-sided Type I error rate of 0.05
- 10% of the patients will not complete 48 weeks of treatment
- A difference of 2 points between the change in mFARS in the RTA 408 and placebo groups
- Standard deviation of change in mFARS of 3.5 points

Since Part 1 and Part 2 are independent sets of patients, the Part 1 analysis will not impact the type I error rate for the Part 2 analysis.

The sample size for the extension is limited to the number of patients having completed Part 1 or Part 2.

Statistical analysis: Separate statistical analysis plans (SAPs) detailing the analyses to be performed will be developed prior to the database lock for each study part. The SAP, which will describe in detail the methods used for the primary and secondary endpoints, will serve as the final arbiter of all statistical analyses. Data will be summarized using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

Primary efficacy analysis: Part 1 and Part 2 will be analyzed separately. Primary analysis of the efficacy data will be based on the intent-to-treat (ITT) population, which will include all patients randomized within each part of the study. Mixed-model repeated measures (MMRM) analysis will be used to analyze the Part 1 and Part 2 primary and secondary efficacy endpoints. The primary analyses of efficacy with MMRM are expected to be at least as powerful as the 2-sided t-test calculations used for study planning.

Extension analysis of safety: As the extension is of an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (i.e., RTA 408 or placebo).

Benefit-Risk Assessment:

Treatment with RTA 408 (omaveloxolone) provides the possibility of benefit based on the efficacy of omaveloxolone previously demonstrated in the present Study 408-C-1402, involving adult and adolescent participants with Friedreich's ataxia aged 16 years and older.

The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with omaveloxolone may be found in the Investigator's Brochure.

The potential risks related to participation in this study are justified by the anticipated benefit to participants. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study assessments and procedures.

All safety findings will be closely monitored and reviewed by a DSMB in Part 1 and Part 2, and by the Sponsor during the extension phase of the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 1: List of Abbreviations

Abbreviation	Explanation
9-HPT	9-hole peg test
ADL	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma drug concentration-time curve
BMI	body mass index
BNP	B-type natriuretic peptide
BORG	Maximum rating of perceived exertion
BUN	blood urea nitrogen
CDDO	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid
CDDO-EA	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid ethylamide
CDDO-Im	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid imidazole
CDDO-Me	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid methyl ester
CDDO-TFEA	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid trifluoroethylamide
CFR	Code of Federal Regulations
C_{max}	maximum analyte concentration in plasma
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
DLT	dose-limiting toxicity
DSMB	data safety monitoring board
DTPA	diethylenetriamine penta-acetic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate

Abbreviation	Explanation
EU	European Union
EU CT	EU Clinical Trials
FARS	Friedreich's ataxia rating scale
FDA	Food and Drug Administration
FEV	forced expiration volume with one second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GRE-EPI	gradient echo–echo planar
GSTA3	glutathione S-transferase A3
HDL-C	high-density lipoprotein cholesterol
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HO-1	heme oxygenase-1
ICF	informed consent form
ICH E6(R1)	International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)
IFNγ	interferon-gamma
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
Keap1	Kelch-like ECH-associated protein 1
Keap1MuKO	Keap1 gene hypomorphic knockdown in mice
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LV	left ventricle
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Explanation
mFARS	modified Friedreich's Ataxia Rating Scale
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
MVV	maximum voluntary ventilation
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
NQO1	NAD(P)H dehydrogenase, quinone 1
Nrf2	nuclear factor erythroid-derived 2-related factor 2
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
PD	pharmacodynamic(s)
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PK	pharmacokinetic(s)
RBC	red blood cell
ROS	reactive oxygen species
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SF-36	SF-36® Health Survey Update
SOD1	superoxide dismutase 1
SpO2	oxygen saturation by pulse oximeter
T1	longitudinal relaxation time constant
TBL	total bilirubin
TE	echo times
T_{max}	time to maximum analyte concentration in plasma
TSENSE	temporal sensitivity encoding
ULN	upper limit of normal
US	United States
US CFR Title 21	Title 21 of the US Code of Federal Regulations
VLDL-C	very-low-density lipoprotein cholesterol
VO2	resting minute oxygen consumption
WBC	white blood cell

Abbreviation	Explanation
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background and Rationale for RTA 408 in Friedreich's Ataxia

Friedreich's ataxia is an autosomal recessive cerebellar ataxia caused by triplet-repeat expansions. The causative mutation is a trinucleotide (GAA) repeat expansion in the first intron of the frataxin gene, leading to impaired transcription of frataxin. Frataxin is involved in iron homeostasis and may protect mitochondria from oxidative damage. Consequently, frataxin mutations result in a phenotype of mitochondrial iron overload and oxidative stress. The pathological consequences of frataxin deficiency include a severe disruption of iron–sulfur cluster biosynthesis, mitochondrial iron overload coupled to cellular iron dysregulation, and an increased sensitivity to oxidative stress [Dürr 2002]. The majority of patients have disease onset before 15 years of age, with a mean duration until wheelchair use of 11 to 14 years after disease onset and a median survival of 34 to 37 years after disease onset [Klockgether 1998].

On 28 February 2023, the United States Food and Drug Administration (FDA) approved omaveloxolone for treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. The drug is now commercially available under the brand name SKYCLARYS®. On 09 February 2024, the European Medicines Agency (EMA) also approved omaveloxolone for the same indication. Additionally, omaveloxolone was approved for treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older in the following countries: Switzerland on 24 September 2024, United Arab Emirates on 30 October 2024, Kingdom of Bahrain on 25 November 2024, Chile on 06 January 2025, Kingdom of Saudi Arabia on 16 February 2025, Sultanate of Oman on 04 March 2025, State of Qatar on 12 March 2025, and Canada on 13 March 2025. No other effective therapies have been approved for the treatment of Friedreich's ataxia. Clinical trials with weak exogenous antioxidants, such as coenzyme Q10 derivatives, and various antioxidant cocktails containing supplements, such as vitamin E (or derivatives), have not resulted in physiological improvements nor have they affected disease progression [Marmolino 2011]. Notably, prior clinical studies with exogenous antioxidants were unable to reduce the excess reactive oxygen species (ROS) produced by the dysfunctional iron homeostasis and resulting mitochondrial damage [Di Prospero 2007].

A hallmark of Friedreich's ataxia is impairment of antioxidative defense mechanisms, which play a major role in disease progression. Studies have demonstrated that nuclear factor erythroid-derived 2-related factor 2 (Nrf2) is impaired in cells isolated from patients with Friedreich's ataxia. Similar findings have been observed in preclinical studies (*in vitro* and *in vivo*). When fibroblasts isolated from patients with Friedreich's ataxia are challenged with agents that induce oxidative stress (e.g., tertiary butylhydroquinone or oligomycin), Nrf2 fails to activate, which, in turn, prevents induction of antioxidant Nrf2 target genes [Paupe 2009]. Further, silencing of frataxin gene expression in mouse motor neuron cells also decreases expression of Nrf2 and its target genes. When frataxin was knocked down approximately 40% by short hairpin RNA in mouse NSC34 motor neurons, Nrf2 mRNA expression was also decreased approximately 35%, along with the protein expression of the Nrf2 target genes superoxide dismutase and glutathione S-transferase π [D'Oria 2013]. Collectively, the data demonstrate that Nrf2 signaling is grossly impaired in patients with Friedreich's ataxia and in preclinical *in vitro* and *in vivo* models of frataxin deficiency. Therefore, the ability of RTA 408 to activate Nrf2 and induce its target genes is hypothesized to be therapeutic in patients with Friedreich's ataxia.

Several lines of evidence suggest that Nrf2 activation can increase mitochondrial respiration and biogenesis. First, activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in a mouse model of mitochondrial myopathy showed increased mitochondrial mass and improved adenosine triphosphate (ATP) production. In addition, Uruno et al. [Uruno 2013] demonstrated that genetic activation of Nrf2 signaling by Kelch-like ECH-associated protein 1 (Keap1) gene hypomorphic knockdown in mice (Keap1MuKO) markedly increased energy consumption–related genes in skeletal muscle. Genetic Nrf2 activation led to increased locomotor activity, as compared with control (Keap1F/F) mice. Locomotor activity was increased as determined in an open-field test and quantitated in terms of total distance traveled, as well as the number of zones crossed during the testing period (0 to 20 min). These results suggest that activation of Nrf2 in skeletal muscle results in locomotor improvement due to increased efficiency of oxidative phosphorylation.

Moreover, 2 recent studies demonstrated that genetic Nrf2 activation in Keap1-knockout mice increased mitochondrial respiration, oxygen consumption, and ATP production compared with Nrf2-deficient mice [Holmström 2013; Ludtmann 2014]. In essence, Nrf2 activation increased substrate availability for mitochondrial respiration, which led to improvements in ATP production.

Natural triterpenoids, such as oleanolic acid and ursolic acid that are derived from plant extracts, have been used extensively in Asian medicine for their antioxidant, anti-inflammatory, and anticancer properties [Liu 1995]. RTA 408 is one of a class of semi-synthetic triterpenoids discovered through a medicinal chemistry effort to optimize the ability of these compounds to inhibit the induction of nitric oxide (NO) in primary mouse macrophages treated with interferon-gamma (IFNγ; [Honda 1999]). Subsequent mechanistic studies have revealed that RTA 408 and the semi-synthetic triterpenoids are potent activators of Nrf2 and inhibitors of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and thus induce an antioxidant and anti-inflammatory phenotype.

Several preclinical studies have highlighted the beneficial effects of RTA 408 analogs on muscle function, oxidative phosphorylation, and mitochondrial biogenesis. Shin et al. [Shin 2009] demonstrated that potent Nrf2 activation with a 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO)-imidazolide (CDDO-Im) triterpenoid prevented high-fat diet-induced increases in body weight, adipose mass, and hepatic lipid accumulation in wild-type mice. Wild-type mice on a high-fat diet and treated with CDDO-Im exhibited higher oxygen consumption and energy expenditure than vehicle-treated mice, while food intake was lower in CDDO-Im-treated than vehicle-treated mice. These results highlight the ability of potent Nrf2 activation to increase mitochondrial respiration.

Saha et al. [Saha 2010] demonstrated that in high-fat diet-fed type 2 diabetic mice, oral treatment with the RTA 408 analog, bardoxolone methyl (also referred to as CDDO-methyl ester [CDDO-Me]), for 2 weeks improved glucose uptake, fatty acid oxidation, and oxygen consumption. Specifically, treatment with bardoxolone methyl led to a 48% increase in the mean glucose disposal rate, reflecting increased peripheral insulin responsiveness induced by bardoxolone methyl. The bardoxolone methyl treatment also increased insulin-stimulated glucose transport activity in skeletal muscles by 71% in the soleus and by 58% in the gastrocnemius. These results demonstrate that the glucose-lowering activity of bardoxolone

methyl results from enhanced insulin action and glucose delivery to the muscles, which was associated with an increased rate of oxidative phosphorylation within the skeletal muscle.

Furthermore, Neymotin et al. [Neymotin 2011] examined 2 additional RTA 408 analogs, CDDO-ethylamide (CDDO-EA) and CDDO-trifluoroethylamide (CDDO-TFEA), that potently activate Nrf2 in the G93A superoxide dismutase 1 (SOD1) mouse model of amyotrophic lateral sclerosis (ALS). CDDO-EA and CDDO-TFEA significantly induced the mRNA expression of the Nrf2 target genes NAD(P)H dehydrogenase, quinone 1 (NQO1), glutathione S-transferase A3 (GSTA3), and heme oxygenase-1 (HO-1) relative to controls while suppressing pro-inflammatory NF-κB target genes. Moreover, genes associated with increased mitochondrial biogenesis were also induced. Collectively, the data suggest that the ability of RTA 408 to activate Nrf2 and induce its target genes could potentially improve muscle function, oxidative phosphorylation, antioxidant capacity, and mitochondrial biogenesis in patients with Friedreich's ataxia.

Regarding the safety profile of RTA 408, no adverse effects were observed in the safety pharmacology studies. The genotoxicity potential of RTA 408 was investigated in 2 *in vitro* genetic toxicity tests and 2 *in vivo* genotoxicity studies in rats. The overall weight of evidence from the genotoxicity studies indicates that RTA 408 has a low genotoxicity risk to human patients.

The systemic toxicity potential of RTA 408 has been evaluated in multiple nonclinical Good Laboratory Practice (GLP) toxicity studies in rats, minipigs, and monkeys after oral and dermal (which produces meaningful systemic exposure to RTA 408 in animals) administration. The primary target organs for RTA 408 observed in the rat and monkey include the liver (increased liver weight, hepatocellular hypertrophy, bile duct hypertrophy and hyperplasia) and kidney (tubular degeneration/regeneration). These effects are considered to be mostly due to the known pharmacologic activity of RTA 408 in animals and likely do not reflect off-target toxicity. In rats (but not monkeys or minipigs), minimal to mild squamous cell hyperplasia of the forestomach and/or the limiting ridge of the stomach was observed and was fully reversible on treatment discontinuation. The forestomach and limiting ridge of the stomach do not exist in humans, a monogastric species. Therefore, this finding does not translate to humans and is not considered a relevant risk to humans.

Overall, rats are more sensitive to the toxicologic effects of RTA 408 than minipigs or monkeys. In rats, the no-observed-adverse-effect level (NOAEL) following 28 days or 13 weeks or daily oral administration was 3 mg/kg/day, corresponding to an area under the plasma drug concentration-time curve ($AUC_{(0\text{-}24hr)}$) of approximately 2.0 hr*µg/mL. Following 6 months of oral administration to rats, adverse effects were observed at the lowest dose tested (0.3 mg/kg), which was associated with an $AUC_{(0\text{-}24hr)}$ of approximately 0.3 hr*µg/mL. Similar systemic exposure was achieved in rats at the lowest dose tested in a 13-week topical dermal toxicity study of RTA 408 Lotion, with similar adverse effects observed in males, but not females, in the low-dose group. In monkeys, the NOAEL following 28 days or 13 weeks of daily oral administration was at least 100 mg/kg/day and the NOAEL following 9 months of daily oral administration was 30 mg/kg/day, corresponding to an $AUC_{(0\text{-}24hr)}$ of approximately 2.0 hr*µg/mL. In a 13-week minipig dermal GLP toxicity study, the NOAEL was the maximal feasible dose of 8% RTA 408 Lotion (twice daily topical administration) with systemic exposures up to 1.7 hr*µg/mL.

Across studies, the adverse liver findings in rats were reversible upon drug discontinuation and were associated with moderate to marked increases in serum gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBL). With short treatment duration (i.e., 14 days), tubular degeneration/regeneration in rats was reversible with a 28-day treatment-free period in a non-GLP study. Although the kidney findings in rats after 28 days or longer of treatment were not reversible after a 4-week or 8-week recovery period, they were minimal to mild, were not associated with evidence of an effect on renal function (i.e., no increase in blood urea nitrogen [BUN] or serum creatinine), and were not present in minipigs or monkeys with dosing for up to 13 weeks (minipig dermal) or 9 months (monkey oral) at doses that produced systemic exposures approximately 10-fold above the exposures that elicited adverse kidney findings in rats.

Patients with the disease of interest were not involved in the design of the study.

5.2. Benefit-Risk Assessment

Treatment with RTA 408 (omaveloxolone) provides the possibility of benefit based on the efficacy of omaveloxolone previously demonstrated in the present Study 408-C-1402, involving adult and adolescent participants with Friedreich's ataxia aged 16 years and older.

The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with omaveloxolone may be found in the Investigator's Brochure.

The potential risks related to participation in this study are justified by the anticipated benefit to participants. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study assessments and procedures.

All safety findings will be closely monitored and reviewed by a data safety monitoring board (DSMB) in Part 1 and Part 2, and by the Sponsor during the extension phase of the study.

6. STUDY OBJECTIVES AND PURPOSE

In patients with Friedreich's ataxia, comparing those receiving RTA 408 versus those receiving placebo, the objectives are as follows:

6.1. Part 1 Objectives

6.1.1. Primary Objectives

- To evaluate the change in peak work during maximal exercise testing
- To evaluate the safety and tolerability of RTA 408

6.1.2. Secondary Objective

- To evaluate the change in the modified Friedreich's ataxia rating scale (mFARS) score

6.1.3. Exploratory Objectives

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in performance on a 25-foot timed walk test
- To evaluate the change in performance on a low-contrast letter visual acuity test
- To evaluate the change in performance on a 9-hole peg test (9-HPT)
- To evaluate the change in Fatigue Severity Scale score
- To evaluate the change in SF-36® Health Survey Update (SF-36) score
- To evaluate the change in the full Friedreich's ataxia rating scale (FARS) score
- [redacted]
- [redacted]
- To evaluate the change in pharmacodynamic (PD) markers of activity in platelet, [redacted] samples
- To characterize the pharmacokinetics (PK) of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules

6.2. Part 2 Objectives

6.2.1. Primary Objectives

- To evaluate the change in the mFARS score at Week 48

- To evaluate the safety and tolerability of RTA 408

6.2.2. Secondary Objective

- To evaluate the change in peak work during maximal exercise testing at Week 48
- To evaluate the Patient Global Impression of Change at Week 48
- To evaluate the Clinical Global Impression of Change at Week 48

6.2.3. Exploratory Objectives

- To evaluate the distribution of change in mFARS scores at Week 48
- To evaluate the change in SF-36 score
- To evaluate the change in performance on a 9-HPT
- To evaluate the change in performance on a 25-foot timed walk test
- To evaluate the change in the Activities of Daily Living (ADL) score
- To evaluate the frequency of falls
- To characterize the PK of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules

6.3. Extension

The objective of the extension is to provide continuing treatment with RTA 408 as part of this extended access program while collecting ongoing safety and tolerability data with RTA 408.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study will evaluate the efficacy, safety, and PD of RTA 408 in the treatment of patients with Friedreich's ataxia. A schema summarizing the study parts and cohorts is shown in Figure 1 and Figure 2.

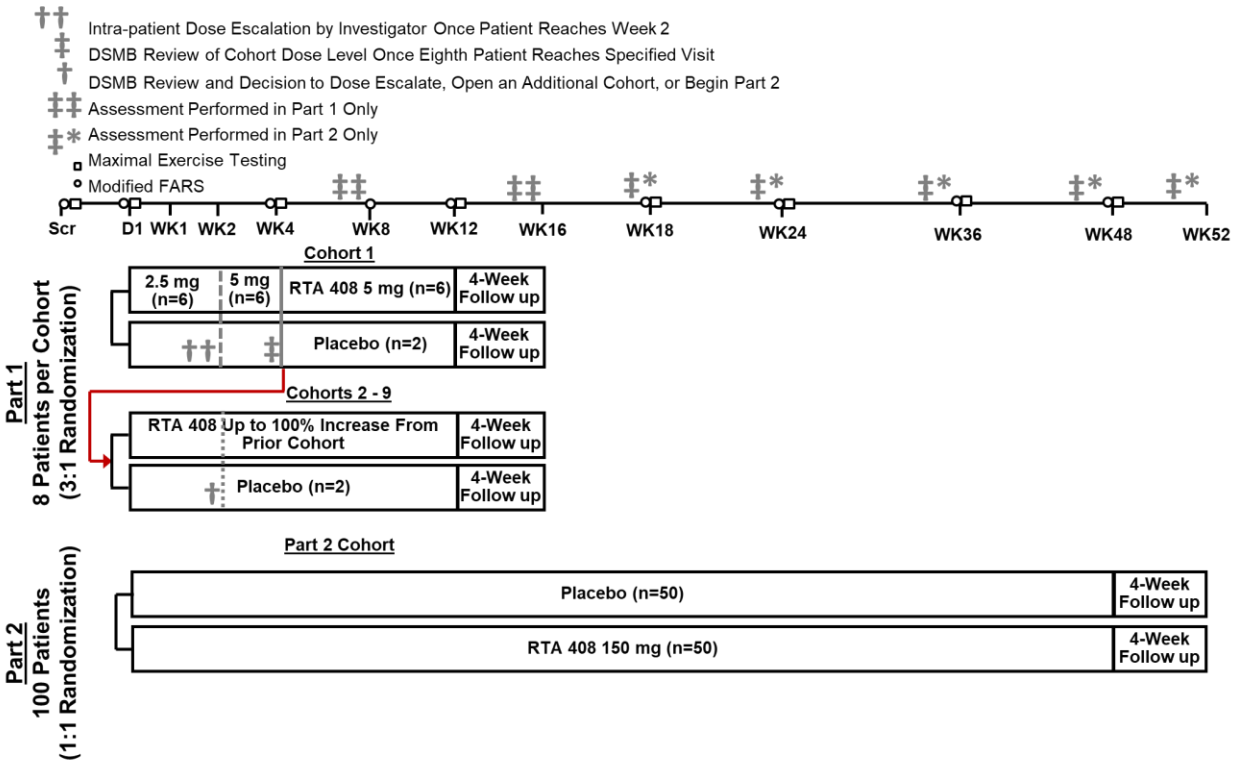
Part 1: The first part of the study will be a randomized, placebo-controlled, double-blind, dose-ranging study to evaluate the safety, efficacy, and PD activity of RTA 408 at 2.5 mg, 5 mg, 10 mg, 20 mg, and higher dose levels (not to exceed 300 mg) in patients with Friedreich's ataxia. A cohort consists of the next eight eligible patients randomized 3:1 to RTA 408 at the cohort specific dose (n=6) or placebo (n=2). Up to approximately 9 cohorts will be enrolled in Part 1 of the study to allow for adequate dose-ranging for selection of a dose of RTA 408 to be used in Part 2.

Intra-patient dose-escalation will only be utilized in the first cohort to evaluate RTA 408 at the first two dose levels (2.5 mg and 5 mg). Patients enrolling in the first cohort will be randomized to RTA 408 2.5 mg or placebo. After the Week 2 visit, each patient in the first cohort will dose-escalate to 5 mg (or remain on placebo) on Day 15 unless a dose-limiting toxicity (DLT) is reported in that patient (Section 7.4.3). After the last patient in the first cohort completes their Week 4 visit (i.e., 2 weeks on 2.5 mg daily [or matching placebo] followed by 2 weeks on 5 mg daily [or matching placebo]), the DSMB and Sponsor will review all available safety information and make a decision regarding enrollment of the next cohort.

Beginning with the second 8-patient cohort, once the eighth patient enrolled completes their Week 2 visit, the DSMB will review all available safety information and recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is 300 mg. The dose level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data. Prior to opening each cohort in Part 1 for enrollment, the Sponsor will evaluate all available data from doses studied in Part 1 to determine if enough information is available to select doses for Part 2 of the study. Once enrollment begins in Part 2, no additional cohorts will be enrolled in Part 1.

Part 2: The second part of this study will be a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of RTA 408 150 mg in patients with Friedreich's ataxia. Patients enrolled in Part 2 will be randomized 1:1 to receive RTA 408 150 mg, or placebo. Randomization will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will comprise no more than 20% of patients enrolled in Part 2. The RTA 408 dose of 150 mg was selected for Part 2 based on DSMB and Sponsor review of available data from Part 1, including safety, efficacy, PK, and PD data. Following randomization on Day 1, patients will self-administer study treatment once daily for 48 weeks. A follow-up visit for safety will occur at Week 52 (4 weeks after last dose). The DSMB will perform quarterly reviews of unblinded data for safety throughout Part 2.

Figure 1: Schema for Part 1 and Part 2 Evaluation of RTA 408 in Patients with Friedreich's Ataxia



Extension: The extension will assess long-term safety and tolerability of RTA 408 in qualified patients with Friedreich's ataxia following completion of Part 1 or Part 2. Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study.

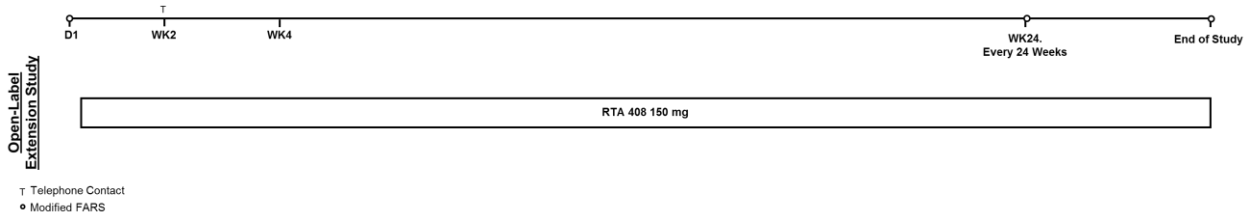
Patients will receive open-label RTA 408 (150 mg) once daily and with extended access until the drug is available through commercial channels or alternate post-trial access mechanisms, or until patient withdrawal, whichever is sooner. All patients in the extension will follow the same visit and assessment schedule. Extension Day 1 is defined as the first day treatment is dispensed to the patient for the extension, following completion of Part 1 or Part 2. All other extension visits will be relative to extension Day 1. Patients will be scheduled for in-person assessments during treatment in the extension at Day 1, Week 4, Week 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Day 14.

Since Part 2 patients will be followed continuously within the study, eligibility for the extension should be assessed at the Week 52 visit and a separate screening visit is not required. After confirming eligibility for Part 2 patients, study treatment for extension Day 1 should be dispensed following the Week 52 assessments. Part 1 patients will not have been followed continuously within this study and therefore must complete a screening visit to confirm eligibility.

The conduct of the extension phase, according to protocol specifications, was impacted by the Coronavirus Disease 2019 (COVID-19) pandemic. As a result, and as of Version 10 of the protocol, modifications intended to address access to and administration of investigational

product, and adherence to protocol-specified visits and laboratory assessments was implemented. These modifications are described in Appendix 13 (COVID-19 Mitigations).

Figure 2: Schema for Open-Label Extension



7.2. Number of Patients

Up to approximately 172 patients will be enrolled in this study (up to 72 patients in Part 1 and approximately 100 patients in Part 2).

The extension will only include qualified patients from Part 1 and Part 2, as outlined in Section 8.3.

7.3. Treatment Assignment

Part 1: Patients enrolled in the first cohort for Part 1 will be randomized 3:1 to receive RTA 408 2.5 mg or placebo. After the Week 2 visit, patients receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg starting on Day 15 unless a DLT is observed. Intra-patient dose-escalation will only be utilized in the first cohort for Part 1. Starting with the second cohort for Part 1, patients will be randomized 3:1 to receive the cohort specific dose level of RTA 408 or placebo and will remain on the same treatment assignment throughout the study.

Part 2: One dose level of RTA 408 within the dose-range evaluated in Part 1 will be used in Part 2. Patients enrolled in Part 2 of the study will be randomized 1:1 to RTA 408 150 mg or placebo. Part 2 randomization will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will not comprise more than 20% of patients enrolled in Part 2.

All randomizations will be performed using an Interactive Web Response System (IWRS).

Extension: All patients in the extension will be assigned to RTA 408 150 mg.

7.4. Dose Selection and Escalation Scheme

7.4.1. Selection of Doses

Part 1: The safety, efficacy, and PD of RTA 408 at multiple dose levels (2.5, 5, 10, 20, 40, 80, 160, and 300 mg) will be evaluated in Part 1 to identify an appropriate dose for Part 2.

Part 2 and Extension: No DLT was observed in Part 1 and a dose of 150 mg was selected for Part 2 and Extension. From the doses evaluated in Part 1, the 160-mg dose of RTA 408 was considered optimal based on DSMB and Sponsor assessment of available safety, efficacy, PK, and PD data. Available capsule strengths of RTA 408 (2.5-, 10-, and 50-mg capsules) require four capsules daily for a 160-mg dose and 3 capsules daily for a 150-mg dose. Available PK data

from Part 1 demonstrate that systemic exposure to RTA 408 is reasonably linear with dose, with modest inter-subject variability (e.g., AUC CV% of approximately 14 to 40%). Consequently, a 150-mg dose, is anticipated to provide similar drug exposure as the 160-mg dose. Based on these considerations, an RTA 408 dose of 150 mg was selected for Part 2 and Extension because it differs by less than 10% from the 160-mg dose that was evaluated in Part 1 and therefore is expected to provide similar systemic exposure while affording a reduction in the number and complexity of capsules that patients are required to swallow once each day for 48 weeks during Part 2 and Extension.

7.4.2. Dose-Escalation Scheme

Part 1: In Part 1 of the study, an initial cohort of 8 patients will be randomized 3:1 to RTA 408 2.5 mg (n=6) or placebo (n=2). Each patient in the first cohort will be evaluated for intra-patient dose-escalation by their investigator at the Week 2 visit. If no DLTs are observed by Week 2 for that patient, the patient will dose escalate. The patients receiving RTA 408 2.5 mg will begin receiving RTA 408 5 mg on Day 15 and the patients receiving placebo will remain on placebo in a blinded fashion. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. Patients who are deemed inappropriate for dose escalation will continue on their originally randomized dose (i.e., 2.5 mg or placebo) throughout the remainder of the study. After the last patient in the initial cohort completes their Week 4 visit, the DSMB and Sponsor will review all available safety information from this cohort and make a recommendation regarding opening the next cohort to be randomized 3:1 to the cohort specific dose level of RTA 408 or placebo. All subsequent cohorts in Part 1, beginning with the second 8-patient cohort, will be evaluated for safety of the cohort-specific dose level by the DSMB once the eighth patient enrolled completes their Week 2 visit. The DSMB will recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study (not to exceed 300 mg). The dose level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data.

Part 2: Dose-escalation or de-escalation will not be used in Part 2. Patients randomized to RTA 408 will receive 150 mg of RTA 408 daily throughout the 48-week treatment period.

Extension: Dose-escalation or de-escalation will not be used in the extension portion of the study. Patients will receive 150 mg of RTA 408 daily throughout participation in the extension.

7.4.3. Criteria for Determining Dose-Limiting Toxicity

Part 1: For the purpose of intra-patient dose escalation in Cohort 1, the assessment of a DLT (i.e., a side effect serious enough to prevent an increase in dose) will be based on the clinical judgment of the investigator. Suspected DLTs should be discussed with the medical monitor. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. All other patients enrolled in Part 1 will remain at a constant dose throughout the 12-week treatment period.

Part 2 and Extension: Dose-escalation is not being used in Part 2 and side effects should be recorded as AEs.

7.4.4. Intra-Patient Dose Escalation

Intra-patient dose escalation will only occur for the first cohort of 8 patients randomized in Part 1 of the study (i.e., those patients randomized to RTA 408 2.5 mg or placebo). Investigators, and not the DSMB, will make intra-patient dose-escalation decisions during the first cohort of Part 1. Each patient will dose escalate starting on Day 15, unless a DLT is indicated by the investigator. Patients originally randomized to RTA 408 2.5 mg will dose escalate to RTA 408 5 mg, and those randomized to placebo will remain on placebo in a blinded fashion. If the investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. If the investigator determines the patient should not be dose escalated, that patient should continue on their originally randomized dose (i.e., 2.5 mg or placebo) throughout the remainder of the study visits.

No other patients are eligible for intra-patient dose escalation.

7.4.5. Additional Considerations for Dose Escalation Decisions in Part 1

A maximum dose of 300 mg may be tested in Part 1 of this study; however, each dose escalation is limited to a 100% increase from the previous dose. If the Sponsor or DSMB considers dose escalation not safe for any reason, no more dose escalation will be carried out. The DSMB may recommend stopping dose escalation at any time, particularly if their review of AEs or laboratory data (e.g., AST, ALT, bilirubin, alkaline phosphatase (ALP), magnesium, creatinine, B-type natriuretic peptide [BNP], etc.), reveals any potential safety concern. The Sponsor, in addition to reviewing all available safety and efficacy data, will also take into consideration the predicted systemic exposure to RTA 408 at the next proposed dose in comparison with the exposure vs adverse effect profile for RTA 408 in animals. If systemic exposure is sufficiently high to warrant a potential concern based on animal toxicity data, dose escalation may be stopped or paused, if needed, to seek additional input from the DSMB or United States Food and Drug Administration (US FDA).

7.5. Data Safety Monitoring Board

A DSMB will review unblinded safety data throughout the study (i.e., Part 1, Part 2) and make recommendations as appropriate. The DSMB will begin monthly data reviews approximately 1 month after the first patient is enrolled in Part 1 through the last dose of the last patient enrolled in Part 1. Part 2 data will be reviewed on a quarterly basis by the DSMB. After the last patient completes Part 2, the DSMB will determine if regular meetings are necessary or may convert to less frequent reviews to align better with the extension schedule of every 24-week visits. Safety data of the open-label extension study is overseen by Reata's internal safety management team.

The DSMB will consist of external clinical experts supported by an independent statistical group. The independent statistical group will prepare unblinded analyses for the DSMB and will not have a role in the statistical analysis plan (SAP) after Part 2 of the study has started enrolling patients. A separate, blinded statistical group will be responsible for producing and finalizing the SAP and executing final data analysis for each part of the study.

The DSMB will be governed by a charter that will describe the following:

- Roles and responsibilities of the DSMB members and the independent statistical group
- Meeting format and frequency
- Communication channels between the DSMB, the independent statistical group, the Sponsor, and the blinded study statisticians
- Voting process and requirements (e.g., requirement of consensus for issuance of a termination recommendation)
- Provisions governing conflict of interest and confidentiality

Briefly, the DSMB will review the progress of the study and the accumulating unblinded data while the study is ongoing. At each data review, the DSMB will assess safety, as evaluated by AEs, laboratory data (e.g., AST, ALT, bilirubin, ALP, magnesium, creatinine, BNP, etc.), limited functional assessment data (maximal exercise testing and mFARS score), and changes in other laboratory and vital sign parameters. The DSMB will assess whether the study should be stopped for safety concerns or the informed consent updated to include new safety information. In addition, the DSMB will review serious adverse events (SAEs) from the safety database, including narratives. The DSMB will make recommendations to Sponsor representatives following each meeting. The DSMB may recommend that the study continue as is, be modified to protect patient safety, or be terminated. In addition to the reviews of unblinded study data, the DSMB will participate with the Sponsor in the recommendation to open the 10-mg cohort and higher dosing cohorts for enrollment for Part 1 and opening Part 2 described in Section 7.4.2. However, investigators, and not the DSMB, will make intra-patient dose-escalation decisions during the first cohort of Part 1.

7.6. Start of Study

The start of the study is the date the first participant signs the informed consent form (ICF).

7.7. End of Study and Criteria for Study Termination

7.7.1. End of Study

Patients will receive open-label RTA 408 in this extension, with extended access until the drug is available through commercial channels or alternate post-trial access mechanisms, or until patient withdrawal, whichever is sooner. To complete the study per protocol, patient access through commercial or alternate pathway must be confirmed prior to patient completion of an EOS visit. The EOS visit should be completed within 30 days of the patient's last dose of study drug. Patients should not begin dosing of commercial product until after the EOS visit is completed.

7.7.2. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study treatment will be

discontinued and the investigator will have the responsibility to prescribe any additional therapy to be administered.

7.8. Schedule of Assessments

Table 2, Table 3, and Table 4 lists the overall schedule of assessments for the study.

Table 2: Part 1 Schedule of Assessments

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Study Day/Week	Screening	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 End of treatment		Week 16[a] End of study/ 4-week follow-up
Day Relative to First Dose	-28 to -1[b]	1[c]	7[d] (±3 days)	14[e] (±3 days)	28 (±3 days)	42 (±3 days)	56 (±3 days)	70 (±3 days)	83 (±3 days)	84 (18-48 hr)[f]	112 (±3 days)
Informed consent	X										
Inclusion/Exclusion criteria assessment	X	X									
Demographics and baseline disease characteristics	X										
Prior and concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
Medical history	X										
Height	X										
Echocardiogram	X[g]								X		
Electrocardiogram	X[g]	X		X[h]	X		X		X		X
Vital sign measurements	X	X	X	X	X		X		X	X	X
Weight and BMI	X	X	X	X	X		X		X	X	X
Physical examination	X								X		X
Adverse event collection		X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X[i]	X	X	X	X		X			X	X
Hematology	X[i]	X	X	X	X		X			X	X
Urinalysis and microscopy	X[i]	X	X	X	X		X			X	X
BNP and NT-proBNP[j]	X	X	X	X	X		X			X	X
Hepatitis B and C and HIV[k]	X[i]										
Pregnancy test WOCBP[l]	X[i]	X		X	X		X			X	X
Randomization		X									
Study drug dispensation[m]		X		X	X		X				
Study drug return and pill count / diary[n]				X[o]	X		X			X	
Study drug administration[p]		←---------- X ----------→									
Telephone contact						X		X			
Exercise regimen reporting	X	X			X				X		
Maximal exercise test[q]	X	X			X					X	
Neurologic FARS	X	X			X		X			X	
25-foot timed walk test[r]	X				X		X			X	
Low-contrast letter visual acuity test	X				X		X		X		
9-hole peg test	X				X		X		X		
Fatigue Severity Scale		X							X		
SF-36 Health Survey Update		X							X		
[redacted]		X							X		
[redacted]		X								X	
Platelet collection[s]		X								X	
[redacted]		X								X	
PK analysis				X[v,w]			X[v]			X[v,w]	

Abbreviations: BMI=body mass index; BNP= B-type natriuretic peptide; FARS=Friedreich's ataxia rating scale; HIV=human immunodeficiency virus; hr =hour; [redacted]; NT-proBNP= N-terminal prohormone of B-type natriuretic peptide; PK=pharmacokinetic; WOCBP=women of childbearing potential.

[a] These procedures should be performed for early termination.

[b] Study Day -1 is the day prior to first dose of study drug.

[c] All Day 1 procedures should be performed prior to administration of first dose of study drug.

[d] Assessments for Visit 3 may be collected by a home health nurse visit (at appropriate locations and approved by Sponsor) or at the study center clinic.

[e] Assessments for Visit 4 must be collected at the study center if patients are enrolled in Part 1 of the study.

[f] Visit 10 should be conducted within 18 hours to 48 hours of Visit 9.

[g] For patients with echocardiograms and electrocardiograms collected within 30 days prior to the Screening Visit, the most recent echocardiogram and electrocardiogram can be used to assess cardiac function and patient eligibility.

[h] At Week 2, electrocardiogram is only required for patients in Part 1 of the study.

[i] A home health nurse visit may be used to collect all lab samples required at the Screening Visit.

[j] Patients must be allowed to rest for a minimum period of 1 hour following maximal exercise test before this blood sample is collected (at the same time as all central lab blood draws). This sample should be taken with the patient in the same position (e.g., sitting or semi-recumbent) at all appropriate visits.

[k] Blood samples should be collected for hepatitis B and C and HIV antibodies only in patients lacking evidence of a negative titer in the past year.

[l] Negative serum pregnancy test results are required at the Screening Visit before study enrollment, and negative urine pregnancy test results are required at all other times indicated for continued participation in the study.

[m] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Day 14, Day 56 (Cohort 1; Part 1 only) and Day 84 after the blood collection for predose PK analysis. All other doses can be administered at home. RTA 408 should be administered once daily through Day 84.

[n] A dosing diary check must be performed at study drug return and pill count.

[o] At Week 2, study drug return, pill count, and diary check are only required for patients in the first cohort of Part 1 of the study.

[p] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Days 14, 28 (Part 2 only), 56 (Cohort 1, Part 1 only), and 84 after the blood collection for predose PK analysis. All other doses can be administered at home. RTA 408 should be administered once daily through Day 84.

[q] On study days where multiple assessments are to be completed, the maximal exercise test will be the first functional assessment performed.

[r] 25-foot timed walk test is only required for ambulatory patients. The 25-foot walk testing component of the FARS should be used for the 25-foot timed walk test assessment.

[redacted]

[u] Platelet collection will only be conducted at Sponsor-qualified sites.

[v] For patients enrolled in the first cohort of Part 1 of the study, blood samples for PK analysis at Visit 4 and Visit 7 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 10 should be collected prior to study drug administration.

[w] For patients enrolled in the second and subsequent cohorts of Part 1 of the study, blood samples for PK analysis at Visit 4 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 10 should be collected prior to study drug administration.

Table 3: Part 2 Schedule of Assessments

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Study Day/Week	Screening	Day 1	Week 1 (telephone)	Week 2	Week 4	Week 8 (telephone)	Week 12	Week 18	Week 24	Week 30 (telephone)	Week 36	Week 42 (telephone)	Week 48 End of Treatment	Week 52 [a] End of Study/ 4-week follow-up
Day Relative to First Dose	-60 to -1 [b]	1[c]	7 (±3 days)	14 (±3 days)	28 (±3 days)	56 (±3 days)	84 (±3 days)	126 (±3 days)	168 (±3 days)	210 (±3 days)	252 (±3 days)	294 (±3 days)	336 (±3 days)	364 (±3 days)
Informed consent	X													
Inclusion/Exclusion criteria assessment	X	X												
Demographics and baseline disease characteristics	X													
Pes cavus assessment	X													
Foot X-ray	X[d]													
Prior and concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X													
Height	X													
Echocardiogram	X[e]								X				X	
Electrocardiogram	X[e]			X	X		X	X	X		X		X	X
Vital sign measurements	X	X		X	X		X	X	X		X		X	X
Weight and BMI	X	X		X	X		X	X	X		X		X	X
Physical examination	X								X				X	X
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X[f]	X		X	X		X	X	X		X		X	X
Hematology	X[f]	X		X	X		X	X	X		X		X	X
Urinalysis and microscopy	X[f]	X		X	X		X	X	X		X		X	X
BNP and NT-proBNP[g]	X[f]	X		X	X		X	X	X		X		X	X
Hepatitis B and C and HIV[h]	X[f,h]													
Pregnancy test WOCBP[i]	X[f,i]	X		X	X		X	X	X		X		X	X
Exercise regimen reporting	X	X												
Randomization		X												
Study drug dispensation		X			X		X		X		X			
Study drug return and pill count / diary[j]					X		X		X		X		X	
Study drug administration[k]		←---------- X ---------- →												
Maximal exercise test[l]	X	X			X		X	X	X		X		X	
Neurologic FARS (practice)	X[m]													
Neurologic FARS[n]	X[o]	X[o]			X		X	X	X		X		X	

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Study Day/Week	Screening	Day 1	Week 1 (telephone)	Week 2	Week 4	Week 8 (telephone)	Week 12	Week 18	Week 24	Week 30 (telephone)	Week 36	Week 42 (telephone)	Week 48 End of Treatment	Week 52 [a] End of Study/ 4-week follow-up
Day Relative to First Dose	-60 to -1 [b]	1 [c]	7 (±3 days)	14 (±3 days)	28 (±3 days)	56 (±3 days)	84 (±3 days)	126 (±3 days)	168 (±3 days)	210 (±3 days)	252 (±3 days)	294 (±3 days)	336 (±3 days)	364 (±3 days)
9-hole peg test	X	X							X				X	
25-foot timed walk test	X	X[p]							X[p]				X[p]	
Video Collection of Normal Walking [q]		X							X				X	
SF-36 Health Survey Update		X							X				X	
Activities of Daily Living	X								X		X		X	
Patient Global Impression of Change							X[r]		X[r]		X[r]		X[r]	
Clinical Global Impression of Change							X[r]		X[r]		X[r]		X[r]	
Falls Diary	X[s]	←					X						→	
PK analysis				X[t]			X[u]		X[u]				X[u]	

Abbreviations: BMI=body mass index; BNP= B-type natriuretic peptide; FARS=Friedreich's ataxia rating scale; HIV=human immunodeficiency virus; NT-proBNP=N-terminal prohormone of B-type natriuretic peptide; PK=pharmacokinetic; WOCBP=women of childbearing potential.

[a] These procedures should also be performed in the event of early termination.

[b] Study Day -1 is the day prior to first dose of study drug.

[c] All Day 1 procedures should be performed prior to administration of first dose of study drug.

[d] Only 1 x-ray will be collected during the study. Only x-rays of the right foot will be completed for the foot x-ray assessment. Patients should complete the x-ray foot assessment at Screening; however, if the patient was not able to complete the x-ray foot assessment at Screening, it may be completed during any visit while the patient is participating in the study.

[e] For patients with echocardiograms and electrocardiograms collected within 90 days prior to the Screening Visit, the most recent echocardiogram and electrocardiogram can be used to assess patient eligibility.

[f] A home health nurse visit may be used to collect all lab samples required at the Screening Visit.

[g] Patients must be allowed to rest for a minimum period of 1 hour following maximal exercise test before this blood sample is collected (at the same time as all central lab blood draws). This sample should be taken with the patient in the same position (e.g., sitting or semi-recumbent) at all appropriate visits.

[h] Blood samples should be collected for hepatitis B and C and HIV antibodies only in patients lacking evidence of a negative titer in the past year.

[i] Negative serum pregnancy test results are required at the Screening Visit before study enrollment, and negative urine pregnancy test results are required at all other times indicated for continued participation in the study.

[j] A dosing diary check must be performed at study drug return and pill count.

[k] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Day 14 (Visit 4), Day 84 (Visit 7), Day 168 (Visit 9), and Day 336 (Visit 13) after the blood collection for predose PK analysis. All other doses can be administered at home. Study drug should be administered once daily through Day 336 (Visit 13).

[l] On study days where multiple assessments are to be completed, the maximal exercise test will be the first functional assessment performed.

[m] The practice FARS assessment is not required for patients having completed a FARS assessment within 90 days prior to Screening. The practice FARS assessment must be performed prior to the screening maximal exercise test.

[n] Other than the practice FARS, all FARS assessments must always be performed after the maximal exercise test.

[o] Both Screening and Day 1 mFARS are required to determine patient eligibility.
[p] Video of the 25-foot timed walk test is optional and will be collected only for those patients who provide consent to video.
[q] Patients who consent to video collection of the 25-foot timed walk test will also have video collection during normal walking with a 25-foot (un-timed) walk using his/her normal gait. The normal walk must be performed after the 25-foot timed walk test.
[r] Patients and investigators must complete the patient global impression of change and clinical global impression of change following completion of the neurological FARS exam.
[s] Patients will be provided the fall diary at Screening and must record fall incidents between Screening and Week 48.
[t] Blood samples for PK analysis at Day 14 (Visit 4) should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration.
[u] A single blood sample for PK analysis at Day 84 (Visit 7), Day 168 (Visit 9), and Day 336 (Visit 13) should be collected prior to study drug administration.

Table 4: Extension Schedule of Assessments

Study Day/Week	Screening[a]	Day 1[b]	Week 2 (telephone)	Week 4	Week 24 + Every 24 Weeks[k]	End of Study[k,]
Day Relative to First Dose in Extension	**-30 to -1**	**1**	**14 (±3 days)**	**28 (±3 days)**	**168, 336, 504 etc. (±14 days)**	**Within 30 days after last dose**
Informed consent	X					
Inclusion/Exclusion	X	X				
Pes cavus assessment	X					
Medical history	X					
Adverse event collection		X[c]	X	X	X	X
Prior and Concomitant medications	X	X	X	X	X	X
Weight and BMI	X	X[d]		X	X	X
Vital sign measurements	X	X[d]		X	X	X
Physical examination	X	X[d]		X	X	X
Height	X			X[j]		
Echocardiogram[e]	X					
Electrocardiogram[e]	X					
Clinical Chemistry	X			X	X	X
Hematology	X			X	X	X
Urinalysis and microscopy	X			X	X	X
BNP and NT-proBNP[f]	X			X	X	X
Hepatitis B and C and HIV[g]	X					
Pregnancy test WOCBP[h]	X	X		X	X	X
Dispense study drug		X		X	X	
Study drug return and pill count				X	X	X
Neurologic FARS		X			X	X
Activities of Daily Living		X			X	X
Patient Global Impression of Change					X[i]	
Clinical Global Impression of Change					X[i]	

25-foot Timed Walk Test		X			X	X
9-Hole Peg Test		X			X	X

Abbreviations: BMI=body mass index; BNP= B-type natriuretic peptide; FARS=Friedreich's ataxia rating scale; HIV=human immunodeficiency virus; NT-proBNP= N-terminal prohormone of B-type natriuretic peptide; WOCBP=women of childbearing potential.

[a] The screening visit is only required for Part 1 patients. Assessments collected at Part 2 - Week 48 or Part 2 - Week 52 should be used to assess eligibility for Part 2 patients.

[b] On Day 1, all required procedures should be performed and eligibility confirmed before study drug is dispensed in the extension.

[c] Adverse event assessments on Day 1 should be performed following study drug administration.

[d] For patients enrolled in Part 2 of the study, visit procedures required at Week 52 and also Extension Day 1 should only be performed once since Part 2 Week 52 and Extension Day 1 should occur on the same day.

[e] For patients with echocardiograms and electrocardiograms collected within 90 days prior to the Screening Visit, the most recent echocardiogram and electrocardiogram can be used to assess patient eligibility.

[f] Patients must be allowed to rest for a minimum period of 1 hour following maximal exercise test before this blood sample is collected (at the same time as all central lab blood draws). This sample should be taken with the patient in the same position (e.g., sitting or semi-recumbent) at all appropriate visits.

[g] Blood samples should be collected for hepatitis B and C and HIV antibodies only in patients lacking evidence of a negative titer in the past year.

[h] A serum pregnancy test will be performed at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local health authorities or IRBs/ECs.

[i] Patients and investigators must complete the patient global impression of change and clinical global impression of change following completion of the neurological FARS exam.

[j] Height will be performed at Week 4 for Part 2 patients enrolled in the Extension.

[k] At week 24+ visits and end of study visit patients should be asked whether they had a recent electrocardiogram and/or echocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria (Part 1 and Part 2)

Patients must:

1. Have genetically confirmed Friedreich's ataxia
2. Have an mFARS score ≥ 20 and ≤ 80. The average of the two mFARS values collected at Screening and Day 1 visits must fall within the allowable range, and they must be within 4.5 points of each other
3. Be male or female and ≥ 16 years of age and ≤ 40 years of age
4. Have no changes to their exercise regimen within 30 days prior to Study Day 1 and be willing to remain on the same exercise regimen during the study period
5. Have the ability to complete maximal exercise testing
6. Have adequate kidney function defined as an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula
7. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
8. Be able to swallow capsules
9. Be willing and able to cooperate with all aspects of the protocol
10. Be willing to practice medically acceptable methods of birth control (Section 9.7.2)
11. Provide written informed consent for study participation, approved by the appropriate Institutional Review Board (IRB)

8.2. Patient Exclusion Criteria (Part 1 and Part 2)

Patients must not:

1. Have uncontrolled diabetes (HbA1c > 11.0%)
2. Have a BNP level > 200 pg/mL
3. Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease
    b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
    c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)

   d. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
   e. History of hospitalization for heart failure in the last five years
   f. Cardiac insufficiency, defined as New York Heart Association Class > 2
   g. History of atrial fibrillation
   h. History of unstable arrhythmias
4. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (B or C)
5. Have known or suspected active drug or alcohol abuse, as per investigator judgment
6. Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal (ULN) of AST or ALT. Levels above this threshold are allowable if attributable to muscle injury
7. Have any abnormal laboratory test value or clinically significant pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by study enrollment
8. Have taken any of the following drugs within 7 days prior to Study Day 1 or plan to take any of these drugs during the time of study participation:
   a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
   b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)
   c. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
9. Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, at screening, clinically relevant deviations in laboratory tests including any one of the following:
   a. ALT and/or AST > 1.5-fold ULN,
   b. bilirubin > 1.2-fold ULN,
   c. alkaline phosphatase (ALP) > 2-fold ULN,
   d. albumin < lower limit of normal (LLN)
10. Have participated in any other interventional clinical study within 30 days prior to Study Day 1
11. Have a cognitive impairment that may preclude ability to comply with study procedures
12. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator
13. Have used antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and vitamin E above the recommended daily allowance, within

14 days prior to Study Day 1 or plan to take any of these supplements during the time of study participation

14. Have previously documented mitochondrial respiratory chain disease
15. Have a history of thromboembolic events within the past 5 years
16. Have taken anticoagulant therapy within 30 days prior to Study Day 1
17. Have scheduled surgical treatment for scoliosis or foot deformity during the study
18. Have had significant current suicidal ideation within 1 month prior to Screening Visit as per investigator judgment or any history of suicide attempts
19. Be pregnant or breastfeeding
20. Prior participation in a trial with RTA 408

8.3. Extension Eligibility

Patients must complete 12 weeks of treatment in Part 1, or 48 weeks of treatment in Part 2, have no significant protocol deviations that would, in the opinion of the investigator, deem the patient unsuitable for enrollment in the extension phase of the study, and continue to meet inclusion and exclusion criteria as specified in Appendix 1.

8.4. Patient Rescreening

Patients may repeat the screening procedures to qualify for the study if they have:

- Used antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and vitamin E above the recommended daily allowance, within 14 days prior to Study Day 1 (rescreening may be performed 14 days or more after discontinuation of supplement)
- Used anticoagulant therapy within 30 days prior to Study Day 1 (rescreening may be performed 30 days or more after discontinuation of anticoagulant therapy)
- Participated in any other interventional clinical study within 30 days prior to Study Day 1 (rescreening may be performed 30 days or more after completion of the clinical study)
- An abnormal laboratory test value that may normalize, in the opinion of the investigator (rescreening may be performed once test value is within normal range)
- Modified their exercise regimen within 30 days prior to Study Day 1 (rescreening may be performed 30 days or more after modification of exercise regimen)
- Taken any of the following drugs within 7 days prior to Study Day 1 (rescreening may be performed 7 days or more after discontinuation of the drug):
  - Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
  - Moderate or strong inhibitors or inducers of cytochrome P450 2C8 or 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)

  - Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
- Failed screening because of operational challenges (rescreening may be performed no fewer than 2 weeks from the date of screen failure)
- Failed screening because of mFARS (the absolute difference in mFARS was ≥ 4.5 points between Screening and Day 1)

Patients may repeat the screening procedures once to qualify for Parts 1 and 2 of the study. For the Extension, patients may be rescreened at the discretion of the Sponsor, following discussion with the investigator site.

8.5. Patient Discontinuation and Termination

Patients have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug or terminate the patient from the study. The reason for a patient's withdrawal or discontinuation from the study will be recorded in the electronic case report form (eCRF).

8.5.1. Patient Discontinuation Criteria

Discontinuation refers to a patient stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Occurrence of an AE or change in medical status that leads the investigator to be concerned about the patient's welfare
- Protocol violations
- Administrative reasons (e.g., inability to continue)
- Sponsor termination of the study
- Voluntary withdrawal
- Pregnancy during the study
- Investigator unblinding

Patients must permanently discontinue study drug if any of the following occur:

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than 2 weeks;
- ALT or AST > 3X ULN and TBL > 2X ULN;
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Patients who are discontinued from study drug in Part 1 or Part 2 should still complete all study visits and undergo all scheduled study assessments, if possible.

8.5.2. Patient Termination Criteria

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Administrative reasons (e.g., inability to continue, lost to follow-up)
- Death
- Withdrawal of consent

Patients who terminate the study for any reason may not re-initiate study drug or study assessments at any time.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Part 1: Depending on cohort dose level (or doses selected for part 2) patients will ingest up to 6 capsules of study drug (1 from each bottle included in study treatment kit) daily throughout the study; study drug is described in Section 10.1. Treatment kits containing up to 160 mg of RTA 408 or placebo will include 4 bottles, each containing 30 count of either active or placebo capsules. Treatment kits containing greater than 160 mg of RTA 408 or placebo will be comprised of 6 bottles, each containing 30 count of either active or placebo capsules. To maintain the study blind, treatment kits used in Part 2 will all include the same number of bottles.

Part 2: Patients will ingest 3 capsules daily throughout the study; study drug is described in Section 10.1. Treatment kits containing RTA 408 or placebo will include 3 bottles, each containing 30 count of either active (RTA 408 50 mg) or placebo capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.

Extension: Patients will ingest 3 capsules daily throughout the extension; study drug is described in Section 10.1. Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules or 1 bottle containing 90 count of active (RTA 408 50 mg) capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.

The Sponsor will provide sufficient quantities of study drug to allow for completion of the study.

9.1.1. Management of Elevated Transaminase Levels (ALT and/or AST)

In ongoing clinical trials with RTA 408, transient increases in transaminases and GGT levels have been observed in some patients (refer to the Investigator's Brochure for additional information). Transaminases should be monitored using data from the scheduled lab draws in Part 2 and the extension. Nearly all instances of elevated transaminases are expected to be asymptomatic. Transaminase levels (as well as TBL, GGT, ALP) will be checked within 48 to 72 hours during an unscheduled visit if the following occurs:

- ALT or AST levels > 3X ULN.

Testing will be repeated every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week or until the patient withdraws consent.

Study drug administration will be permanently discontinued if any of the following occurs:

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than 2 weeks;
- ALT or AST > 3X ULN and (TBL > 2X ULN);
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

The hepatobiliary tree must be visualized (e.g., ultrasound, MRI) and assessed if a patient discontinues taking study drug secondary to elevated transaminase levels. Additional tests/studies may be warranted depending on the clinical presentation.

9.2. Prior and Concomitant Medications

9.2.1. Excluded Medications

Patients who have taken any of the following drugs within 30 days prior to Study Day 1 will be excluded from the study:

- Any other investigational drug
- Anticoagulant therapy, with the exception of a daily baby aspirin (up to 81 mg)

Patients who have taken any of the following drugs within 14 days prior to Study Day 1 will be excluded from Part 1 and Part 2:

- Antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and dosages exceeding the recommended daily allowance of vitamin E
- Anti-spasticity agents

Patients who have taken any of the following drugs within 7 days prior to Study Day 1 will be excluded from the study:

- Herbal preparations, minerals, or over-the-counter medication, except as identified in Section 9.2.3
- Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
- Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)
- Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)

9.2.2. Prohibited Medications

The following medications and medication classes are not permitted during Part 1 and Part 2, except as noted in Section 9.2.3:

- Anticoagulant therapy, with the exception of daily baby aspirin (up to 81 mg)
- Antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and dosages exceeding the recommended daily allowance of vitamin E
- Herbal preparations, vitamins, minerals, or over-the-counter medication, except as identified in Section 9.2.3
- Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
- Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)

- Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
- Any interventional therapy intended to treat the Friedreich's ataxia disease condition, with the exception of a constant exercise regimen
- Anti-spasticity agents

The following medications and medication classes are not permitted during the extension study:

- Systemic moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice, cannabidiol, fluvoxamine, verapamil, diltiazem)

If a patient takes a prohibited medication during the study, the investigator should notify the Medical Monitor immediately.

9.2.3. Permitted Medications

The following concomitant medications are permitted, as authorized by the treating physician:

- Antibiotics, except as noted above (Section 9.2.1)
- Daily multivitamin
- Pain medication, except as noted above (Section 9.2.1)
- Other medications intended to manage concurrent diseases, except as noted above (Section 9.2.1)
- Oral, implantable, or injectable contraceptives

The following concomitant medications are permitted only during the extension study:

- Antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and dosages exceeding the recommended daily allowance of vitamin E
- Anti-spasticity agents

Patients taking medication chronically should be maintained on those same doses and dose schedules throughout the study period, as medically feasible. Patients taking medications with intermittent or as-needed schedules should try to avoid taking the concomitant medication on days when PK samples will be collected, as medically feasible.

9.3. Compliance with Study Drug

The investigator or designee will only dispense study drug to patients randomized to study treatment in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

All patients will return all bottles and unused pills and will be dispensed a new kit of study drug at visits indicated in Table 2, Table 3, and Table 4. In addition, patients in the first cohort of Part 1 will return all unused pills at the Week 2 visit and will be dispensed a new kit of study drug at that time. Compliance will be measured by counting pills to determine the number of missed doses from one visit to the next. Patients will also be provided a dosing diary to document that pills were taken as instructed as well as the date and time of dosing

(Section 9.9.23). To be considered compliant with study drug, patients can miss no more than 25% of the total planned doses (i.e., 21 doses during Part 1, or 84 doses during Part 2) during the study. Patients who exceed the number of allowed missed doses will be considered noncompliant with dosing. Patients will not be discontinued from the study drug nor terminated from the study for noncompliance, but protocol deviations should be recorded for dosing noncompliance.

9.4. Randomization

Patients enrolled in Part 1 cohorts will be randomized 3:1 to RTA 408 at the cohort-specific dose level or placebo. Patients enrolled in Part 2 will be randomized 1:1 to RTA 408 150 mg or placebo. Randomization in Part 2 will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will not comprise more than 20% of patients enrolled in Part 2. Randomization for both Part 1 and Part 2 will be generated using a centralized IWRS.

Patients enrolled in the extension will be assigned to RTA 408 150 mg.

9.5. Blinding

To maintain the study blind, all study drug kits will be packaged with blinded labels. Investigators will distribute the blinded study drug kits by kit number to patients as assigned by the IWRS. All patients, investigators, site personnel, and laboratories with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments and appropriate measures will be taken to ensure the blind is maintained to reduce potential bias. Some Sponsor personnel may have access to treatment assignments during dose escalation (Part 1), but during Part 2, all Sponsor personnel will be blinded to treatment assignment.

The only people with access to treatment assignments for Part 2 will be those individuals who maintain the IWRS, the DSMB, the unblinded statistical team providing data to and analyzing data for the DSMB, and safety personnel without direct involvement in the conduct of the study who are assigned to report unblinded data to regulatory authorities as required.

The extension will be considered open-label. All patients in the extension will be assigned RTA 408 150 mg. Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study.

9.5.1. Patient Unblinding

Although there is no known antidote to RTA 408, under rare circumstances, unblinding may be considered medically necessary for safety reasons. Unless faced with a life-threatening medical situation, the investigator should contact the medical monitor to discuss if there is a medically compelling reason to unblind the patient's treatment assignment. After the discussion, the investigator may proceed to unblind the patient, as appropriate. If unblinding is required, the investigator will utilize the IWRS to perform the unblinding. If a study drug assignment is unblinded, a description of the event that required unblinding must be documented by the investigator in the patient's source documents. Patients must discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee), but they should remain blinded and continue attending all study visits and should undergo all study assessments.

Patient treatment assignments must not be unblinded in the case of an AE or SAE, except as described above.

9.5.2. Unblinding for Regulatory Submission

In situations where a regulatory body requires unblinding and reporting of a particular SAE, the appropriate bodies (e.g., ethics committees, IRBs) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to the investigator, site personnel, or patient; therefore, this type of unblinding does not necessitate that the patient discontinue taking study drug.

9.6. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Patient rescreening
- Management of an AE or SAE
- Performance of additional laboratory tests for clinically abnormal test values or to confirm a possible pregnancy
- If the investigator feels that it is clinically appropriate for patient safety

9.7. Pregnancy

9.7.1. Women of Childbearing Potential

Women of childbearing potential (WOCBP) are female patients who are not surgically sterile (no hysterectomy or bilateral salpingo-oophorectomy), have not had reproductive potential terminated by radiation or chemotherapy, and are not postmenopausal for at least 1 year.

9.7.2. Methods of Birth Control

Omaveloxolone is a weak CYP3A4 inducer. Concomitant use with omaveloxolone may reduce the efficacy of hormonal contraceptives; thus, they should not be the sole method of birth control.

During screening, during the treatment period, and until 28 days following administration of the final dose of omaveloxolone, females who are sexually active and of childbearing potential must practice 1 of the following acceptable methods of birth control:

- Use of hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) as prescribed, plus a nonhormonal contraception method (cap, diaphragm, sponge with spermicide, or condom with or without spermicide).
- Use of an intrauterine hormone-releasing system as prescribed, plus a nonhormonal contraception method (cap, diaphragm, sponge with spermicide, or condom with or without spermicide).
- Use of a nonhormonal intrauterine device with appropriate reinsertion period (as prescribed).

- Bilateral tubal occlusion
- Vasectomized partner (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). Partner must be the sole partner for that participant.
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

During screening, during the treatment period, and until 28 days after the final dose of omaveloxolone, fertile males who have female partners of childbearing potential must practice at least 1 of the following methods of birth control:

- Have had a vasectomy (at least 6 months earlier) with documented surgical success (e.g., absence of sperm in the ejaculate).
- Partner contraception methods; must be sole partner for that participant:
  - Use of hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) as prescribed.
  - Use of a nonhormonal intrauterine device with appropriate reinsertion period as prescribed.
  - Use of an intrauterine hormone-releasing system as prescribed.
- Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm).
- Use of condoms with or without spermicide.
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

In addition, participants should not donate sperm or eggs for the duration of the study and for at least 28 days after their last dose of study treatment.

9.7.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male patients must be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the patient must discontinue taking study drug but continue to attend all study visits and undergo all study assessments. The investigator must immediately report a pregnancy associated with study drug exposure and record the event.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient or the pregnant female partner of a male patient (if consenting) and report follow-up information

regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. The Sponsor or its designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

9.8. Treatment Interruption

In the case of serious toxicities, the investigator may choose to interrupt treatment with study drug. If study drug treatment interruption exceeds 21 total days, a protocol deviation should be noted. Dose reductions are not permitted. Patients who are permanently discontinued from study drug for any reason should still complete all Part 1 and Part 2 study visits and undergo all scheduled study assessments, if possible. If the toxicity has resolved such that the investigator does not consider continued drug treatment to be an additional risk to the patient, the investigator may restart study drug treatment. Patients who are permanently discontinued from study drug during the extension should complete the end of study assessments and be terminated from the study.

9.9. Study Procedures

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determination completes all subsequent assessments. All assessments occur in the study center clinic with the exception of those assessments for lab collection at Screening (all patients, Part 1 and Part 2) and Visit 3 (Part 1 only), which may be performed by a home health visit nurse (at appropriate locations and approved by Sponsor) and those assessments for Visits 6 and 8 in Part 1 and Visits 3, 6, 10 and 12 in Part 2, which will be performed via telephone contact. During the extension every effort should be made to ensure patient assessments are performed on-site. If this is not possible home health visits are acceptable. For more detail regarding use of home health services see Appendix 13 (COVID-19 Mitigations).

9.9.1. Informed Consent

Written informed consent (Section 17.3) must be obtained from the patient before any study-related procedures are performed, and if there is a change in the study procedures that could affect the patient's willingness to participate. Patients have the option to separately consent to have video recorded during the 25-foot timed walk and 25-foot normal walk tests at selected sites.

9.9.2. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria should be reviewed at the times indicated in Table 2, Table 3, and Table 4. Patients must meet all of the inclusion criteria and none of the exclusion criteria for

entry into the study. Investigators and/or study site personnel should contact the medical monitor for any questions regarding patient eligibility.

9.9.3. Demographics and Baseline Disease Characteristics

Demographic data, including sex, age, race, and ethnicity, and baseline disease characteristics, including, but not limited to, documentation of genetic confirmation of Friedreich's ataxia and presence or absence of pes cavus, will be collected at the time indicated in Table 3 and Table 4.

9.9.4. Pes Cavus Assessment

The process for classifying pes cavus will be described in a separate study manual. Pes cavus will be assessed at the times indicated in Table 3 and Table 4. Patients who participated in Part 1 of the study must complete a pes cavus assessment at the Extension Study Screening visit (Table 4).

9.9.5. Foot X-Ray

The foot x-ray assessment will be performed to quantify the foot structure of patients with and without pes cavus. Specific radiological angles of the foot will be quantified by a central reader. Radiological angles assessed from a lateral image of the foot may include but are not limited to tibia-talar angle, talo-calcaneal angle, tibia-calcaneal angle, talo-first metatarsal angle, calcaneal pitch angle, and naviculocuboid overlap. The x-ray of the lateral view of the right foot will be collected once per patient at the time indicated in Table 3. Patients should complete the foot x-ray at Screening; however, if a patient was not able to complete the foot x-ray at Screening, it may be completed at any point during the first 52 weeks of the study.

9.9.6. Prior and Concomitant Medications

Information on prior and concomitant medications will be collected at the times indicated in Table 2, Table 3, and Table 4. The name, dose, and frequency of all medications that the patient is taking or has taken within 30 days prior to Study Day 1 must be recorded during the study and until the final visit. All allowed and excluded medications should be recorded, including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used whenever possible.

9.9.7. Medical History

A complete medical history (e.g., per patient report) that includes all medical history within the past 5 years will be collected and recorded at the time indicated in Table 2, Table 3, and Table 4.

9.9.8. Height

Height should be measured without footwear, head coverings, or prosthetics at the time indicated in Table 3 and Table 4.

9.9.9. Echocardiogram

An echocardiogram will be recorded at the times indicated in Table 2, Table 3, and Table 4 after the patient has rested for approximately 10 minutes in a supine position. For patients with echocardiograms collected within 90 days prior to Screening Visit, the most recent

echocardiogram can be used to assess cardiac function and patient eligibility. Patients are ineligible to participate in the study if they have pericardial constriction, restrictive or congestive cardiomyopathy, or left ventricular ejection fraction <40%. However, patients with mild to moderate cardiomyopathy associated with Friedreich's ataxia are not excluded.

Patients from Part 1 of the study that want to participate in the Extension must have an echocardiogram collected within 90 days prior to Extension Day 1.

During the extension, at week 24+ visits and end of study visit, patients should be asked whether they had a recent echocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.

9.9.10. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be recorded at the times indicated in Table 3 and Table 4 after the patient has rested for approximately 10 minutes in a supine position. The heart rate from the ECG machine should not be used as part of the vital sign measurements.

An ECG is required for eligibility. If a patient has had an ECG completed within 90 days prior to the Screening Visit, the most recent ECG can be used as the screening assessment for patient eligibility.

During the extension, at week 24+ visits and end of study visit, patients should be asked whether they had a recent electrocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.

9.9.11. Vital Sign Measurements

Vital sign measurements should be taken at the times indicated in Table 3, Table 4, and Table 5 and include the patient's heart rate (beats/minute), blood pressure (mm Hg), and body temperature (°C or °F). Blood pressure should be taken after the patient has rested in a sitting position for approximately 5 minutes. The same arm (usually the non-dominant arm) and the appropriate size cuff should be used for each measurement.

9.9.12. Weight and Body Mass Index

Weight should be measured at the times indicated in Table 2, Table 3, and Table 4. Body mass index (BMI) will be calculated within the eCRF each time the weight is recorded. If patients are weighed at the Screening Visit with additional leg braces, walkers, or shoes, all additional weight assessments must be conducted with the same appendages.

9.9.13. Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner at the times indicated in Table 3, Table 4, and Table 5. If possible, the same individual should perform each physical examination on a patient during the study. The examination must include the following organ or body system assessments: general appearance, head, eyes, ears, nose, throat, neck, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, dermatologic, extremities, and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Each body system finding must be assessed for clinical significance. Clinically

significant findings at the Screening Visit must be included in the patient's medical history. New clinically significant findings after first dose must be included as AEs. Subsequent assessments beyond screening should be characterized as new, worsening, improved, or unchanged relative to the previous assessment.

9.9.14. Adverse Event Collection

Patients should be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness at the times indicated in Table 3, Table 4, and Table 5. Patients should be instructed to volunteer any information regarding AEs at any time during the study. The study physician or the study staff should also query patients with an open question regarding any AEs they may be experiencing (e.g., "How do you feel?" or "How have you been feeling since your last visit?"). Any findings are to be documented.

9.9.15. Clinical Chemistry

Blood samples will be collected for clinical chemistry analyses at the times indicated in Table 2, Table 3, and Table 4. Clinical chemistry analyses are listed in Table 5. Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator. For calculation of the eGFR, the 4-variable MDRD equation must be used. The equation is as follows:

eGFR = 175 x standardized serum creatinine $^{-1.154}$ x age $^{-0.203}$ x 1.212 [if black] x 0.742 [if female]

Table 5: Clinical Chemistry Assessments

Clinical Chemistry Assessments
Blood urea nitrogen (BUN)
Creatinine
Total bilirubin (TBL)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline phosphatase (ALP)
Ferritin
Sodium
Potassium
Calcium
Inorganic phosphorus
Magnesium
Chloride
Bicarbonate
Uric acid
Cholesterol
Total protein
Glucose
Triglycerides
Albumin
Creatine phosphokinase (CPK)
Creatine kinase isozyme (only if CPK is > ULN)
Lactate dehydrogenase (LDH)
High-density lipoprotein cholesterol (HDL-C)
Low-density lipoprotein cholesterol (LDL-C)
Very-low-density lipoprotein cholesterol (VLDL-C)

Clinical Chemistry Assessments
Gamma-glutamyl transpeptidase (GGT)
Estimated glomerular filtration rate (eGFR) using the MDRD-4 formula

9.9.16. Hematology

Blood samples will be collected for hematology assessments at the times indicated in Table 2, Table 3, and Table 4. Hematology assessments are listed in Table 6. Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator. As noted in Table 6, HbA1c will only be collected at Screening and Week 12 visits.

Table 6: Hematology Assessments

Hematology Assessments
Hematocrit
Hemoglobin
HbA1C (Screening, Week 12)
Red blood cell (RBC) count
White blood cell (WBC) count
Neutrophils
Bands (if detected)
Lymphocytes
Monocytes
Basophils (if detected)
Eosinophils (if detected)
Absolute platelet count
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin concentration (MCHC)
Reticulocyte count

9.9.17. Urinalysis and Microscopy

Urine samples will be collected for urinalysis and microscopy assessments at the times indicated in Table 2, Table 3, and Table 4. Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator. Urinalysis and microscopy assessments are listed in Table 7.

Table 7: Urinalysis/Microscopy Assessments

Urinalysis/Microscopy Assessments
Specific gravity
Ketones
pH
Protein
Blood
Glucose
Urobilinogen
Bilirubin
Microscopic examination (if indicated based on laboratory procedures)
Leukocytes
Nitrates

9.9.18. N-Terminal Prohormone of B-Type Natriuretic Peptide and B-Type Natriuretic Peptide

Blood samples will be collected for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and BNP at the times indicated in Table 3, Table 4, and Table 5 (at the same time as the central lab blood collection). Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator. Since NT-proBNP may be affected by recent exercise, patients must be allowed to rest for a minimum period of 1 hour following study-specific exercise testing prior to obtaining this blood sample. This sample should be taken with the patient in the same position at all appropriate visits (e.g., sitting or semi-recumbent).

9.9.19. Hepatitis B and C and Human Immunodeficiency Virus

Blood samples will be collected for hepatitis B and C and HIV antibody assessments only in patients lacking evidence of a negative titer in the past year at the time indicated in Table 2, Table 3, and Table 4.

9.9.20. Pregnancy Test

WOCBP (Section 9.7.1) will provide a blood or urine sample for a pregnancy test at the times indicated in Table 3, Table 4, and Table 5. Negative serum test results are required at the Screening Visit before study enrollment, and negative urine test results are required at all other times indicated in Table 3, Table 4, and Table 5 for continued participation in the study. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.7.3 for a description of procedures to be followed in case of pregnancy.

9.9.21. Exercise Regimen Reporting

Exercise regimen will be recorded at baseline. Patients will be asked about changes to their exercise regimen at the times indicated in Table 3 and Table 4. Changes to the exercise regimen during Part 1 or Part 2 will be recorded as protocol deviations.

9.9.22. Study Drug Dispensation

Enough study drug will be dispensed to the patient at the times indicated in Table 3, Table 4, and Table 5 to last at least until the next study visit, along with instructions for use.

9.9.23. Study Drug Return and Pill Count

Study drug will be collected from the patient and pills will be counted by the principal investigator or the study staff at the times indicated in Table 3, Table 4, and Table 5 to determine treatment compliance. Criteria for noncompliance and instructions for recording compliance on the eCRF are included in Section 9.3.

Patients will be provided a dosing diary in Part 1 and Part 2 to track all doses administered, including the date and time of each dose. The patient will bring the dosing diary to the clinic to be reviewed by the site staff for study drug accountability.

9.9.24. Study Drug Administration

Part 1: As outlined in Section 9.1, study drug treatment kits will contain up to six 30-count bottles of RTA 408 or placebo capsules. Patients should take 1 capsule from each bottle daily. Patients should self-administer study drug orally once daily in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). Study drug should be taken with water at the times indicated in Table 3, except on Days 1, 14, 56 (Cohort 1; Part 1 only), and 84, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, 56 (Cohort 1; Part 1 only), and 84. The date and time of the 2 most recent doses of study medication prior to Days 14, 56 (Cohort 1; Part 1 only), and 84 will be recorded for PK analysis. The date and time of the last study drug administration (Day 84) should be recorded. A vomited dose should not be replaced. Missed doses may be taken in the afternoon or evening of the same day approximately 1 hour before or 2 hours after a meal. A double dose (e.g., missed dose from previous day and dose for current day) should not be taken.

Part 2: As outlined in Section 9.1, study drug treatment kits will contain three 30-count bottles of RTA 408 or placebo capsules. Patients should self-administer study drug orally once daily in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). Study drug should be taken with water at the times indicated in Table 3, except on Days 1, 14, 84, 168, and 336, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, 84, 168, and 336. The date and time of the 2 most recent doses of study medication prior to Days 14, 84, and 168, will be recorded for PK analysis. The date and time of the last study drug administration (Day 336) should be recorded.

Extension: As outlined in Section 9.1, patients will ingest 3 capsules daily throughout the study. Study drug should be taken with water at the times indicated in Table 4.Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules or 1 bottle containing 90 count of active (RTA 408 50 mg) capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.

A vomited dose should not be replaced. Missed doses may be taken in the afternoon or evening of the same day approximately 1 hour before or 2 hours after a meal. A double dose (e.g., missed dose from previous day and dose for current day) should not be taken.

9.9.25. Telephone Contact

Sites should complete a telephone visit contact with the patient to assess AEs and concomitant medications at the times indicated in Table 2, Table 4, and Table 5. Sites should make at least 3 attempts to contact the patient within the visit window if contact attempts are unsuccessful.

9.9.26. Maximal Exercise Test

Cycle ergometry using a recumbent stationary bicycle will be used to conduct maximal exercise testing at the times indicated in Table 3 and Table 4. An example of the procedures for maximal exercise testing is provided in Appendix 2. Maximal exercise testing assessments include but are not limited to peak work and peak oxygen utilization. On study days where multiple assessments are to be completed, the maximal exercise test must be the first functional assessment performed.

9.9.27. Friedreich's Ataxia Rating Scale

The examiner will complete the full FARS neurological examination on the patient at the times indicated in Table 3, Table 4, and Table 5. An example of the procedures for the FARS assessment is provided in Appendix 3. A practice FARS assessment is included in the schedule of assessments to familiarize those patients who have not recently completed a FARS assessment with the components of the neurological exam. The practice FARS assessment is not required for patients having completed a FARS assessment within 90 days prior to Screening. The practice FARS assessment must be performed prior to the screening maximal exercise test. Other than the practice FARS, all FARS neurological examinations must be performed following maximal exercise testing.

The examiner will need a reflex hammer, tuning fork, and stopwatch. Instructions will be provided in the study manual. The FARS examination should be completed by one of the neurologists at the site delegated to complete this assessment. The individual components of this examination will be recorded so that the mFARS score can be calculated as a subset of the full neurological FARS examination score, as required.

The full neurologic FARS is divided into 5 sections: bulbar, upper limb coordination, lower limb coordination, peripheral nervous system, and upright stability. This examination must be performed and ratings determined by a trained neurologist. As the examiner proceeds through the items, he/she can call out scores to a coordinator or research assistant to record onto the eCRF.

For every item in the FARS exam, a higher score means that the patient is more severely affected. A score of 0 for an item means that the patient has a normal score. Not all of the items have the same possible scoring range. Some of the items will range from 0 to 2, while others will range from 0 to 4. Some items can be scored with 0.5 increments if the examiner feels that the patient falls between 2 defined scoring severities. There are specific instructions for performing assessment of each item and scoring instructions on the eCRF.

The mFARS is not a separate assessment but rather calculated as the full FARS neurological assessment minus section D (peripheral nervous system). The mFARS includes 4 sections: bulbar, upper limb coordination, lower limb coordination, and upright stability.

9.9.28. 9-Hole Peg Test

Patients will take the 9-HPT (Appendix 4) at the times indicated in Table 2, Table 3, and Table 4. Instructions are provided in the study manual.

9.9.29. 25-Foot Timed Walk Test

Ambulatory patients will complete the 25-foot timed walk test at the times indicated in Table 3, Table 4, and Table 5. If a patient uses an assistive device for the 25-foot timed walk test on Day 1, the same assistive device should be used for all 25-foot walk assessments when possible. Patients will have the option to consent to video recording during the 25-foot timed walk test at selected sites. Video recording for the 25-foot timed walk test is optional. Procedures for video collection will be described in a separate study-specific manual.

9.9.30. Video Collection of Patients Walking 25-ft with Their Natural Gait

Patients who consent to video collection of the 25-foot timed walk test will also have video collection during normal walking with a 25-foot (un-timed) walk using his/her normal gait, at the times indicated in Table 4. The normal walk must be performed after the 25-foot timed walk test. Procedures for video collection will be described in a separate study specific manual.

9.9.31. SF-36 Health Survey Update

Patients will be instructed to answer the 36 questions on the SF-36 survey [Jenkinson 1999] according to how they have felt over the previous week, at the times indicated in Table 3 and Table 4. The SF-36 (Appendix 5) assesses 8 health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions.

9.9.32. Activities of Daily Living

Patients will be instructed to answer the 9 questions on the ADL survey at the times indicated in Table 3 and Table 4. The ADL survey (Appendix 6) assesses 9 concepts: (1) speech; (2) swallowing; (3) cutting food and handling utensils; (4) dressing; (5) personal hygiene; (6) falling; (7) walking; (8) quality of sitting position; and (9) bladder function.

9.9.33. Patient Global Impression of Change

The Patient Global Impression of Change is a 7-point scale that requires the patient to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention [Guy 1976]. Patients will be instructed to complete the Patient Global Impression of Change survey at the times indicated in Table 4. The patient global impression of change is assessed by completing the following statement “since I began trial treatment, my

overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).” Patients must complete this assessment following completion of the FARS neurological assessment or the clinical global impression of change.

9.9.34. Clinical Global Impression of Change

The Clinical Global Impression of Change is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention [Guy 1976]. Clinicians will be instructed to complete the Clinician Global Impression of Change survey at the times indicated in Table 4. The clinician global impression of change is assessed by completing the following statement “Compared to the patient’s condition at the start of the trial, this patient’s overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).” Clinicians may take into account prior results of study assessments to influence their clinical judgement of the Clinician Global Impression of Change. Clinicians must complete this assessment following the patient’s completion of the FARS neurological assessment or the patient global impression of change.

9.9.35. Falls Diary

Throughout Part 2 of the study, patients will be instructed to record any instances of falls in a study diary (Table 4). A fall is defined as “the patient unintentionally coming to rest on the ground or at a lower level.” Items included on the falls diary may include but are not limited to the date and time of each fall, the location of the fall, the preceding activity prior to the fall, the perceived cause of the fall, and if an injury was sustained after the fall. Patients will be provided the fall diary at Screening and must record fall incidents between Screening and Week 48.

9.9.36. Pharmacokinetic Analysis (Part 1 and Part 2)

Blood samples for plasma PK analysis will be collected at the times indicated in Table 2 and Table 3. Blood sample collection instructions are detailed in the lab manual. All pre-dose blood samples should be collected within 1 hour prior to dose administration. All other blood samples for PK analysis should be collected ± 15 minutes of the scheduled time.

The date and time of collection of all PK blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations. Sample time deviations will be summarized in the study report. Dates in the eCRF should be recorded in an unambiguous format (e.g., DD MM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not collected should be recorded as such. Detailed sample processing instructions will be provided for isolation, storage, and shipment of plasma PK samples.

9.9.37. Home Health Visits

For Part 1 and Part 2 patients at approved sites will have the option of having a home health visit at the Screening Visit (all patients, Part 1 and Part 2) and Visit 3 (Part 1 only).

During the extension every effort should be made to ensure patient assessments are performed on-site. If this is not possible home health visits are acceptable. For more detail regarding use of home health services see Appendix 13 (COVID-19 Mitigations).

9.9.38. Low-Contrast Letter Visual Acuity Test (Part 1 Only)

The low-contrast letter visual acuity test will be performed at the times indicated in Table 3 (Appendix 7). Instructions are provided in the study manual. Low-contrast letter visual acuity parameters include but are not limited to the number of letters that the patient correctly identifies for each line, the letters the patient missed on each line, contrast level (100%, 2.5%, or 1.25%), chart number, and if the assessments were performed in both eyes or 1 eye. If a patient uses standard vision correction on Day 1, the same vision correction must be used for all low-contrast letter visual acuity assessments. Different charts should be used on different days for each patient.

9.9.39. Fatigue Severity Scale (Part 1 Only)

Patients will be instructed to answer the 9 questions on the Fatigue Severity Scale [Krupp 1989] at the times indicated in Table 3. They will answer according to a recall period over the past week. Patients will assign a number from 1 to 7 that indicates their degree of agreement with each statement (where 1 indicates strong disagreement and 7 indicates strong agreement; (Appendix 10).

[redacted]

9.9.43. Platelet Collection (Part 1 Only)

Platelet collection will be required only at Sponsor-qualified sites. Blood samples for platelet analysis will be collected at the times indicated in Table 3. Blood samples (8.5 mL each) will be collected into 8.5-mL acid-citrate-dextrose Vacutainer® tubes. Procedures for platelet isolation and analysis will be provided in a study manual.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Capsules containing RTA 408 at the 2.5-mg, 10-mg, and 50-mg strengths, or the corresponding placebos, as described in Table 8 will be used in this study.

Table 8: Study Drug Information

Description	RTA 408 Capsule, 2.5 mg, 10 mg, 50 mg	Matching Placebo Capsules
Ingredients	RTA 408, silicified microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, in white opaque, size #4 or #0 capsule shells consisting of hypromellose and titanium dioxide	Silicified microcrystalline cellulose, pregelatinized starch, magnesium stearate, in white opaque, size #4 or #0 capsule shells consisting of hypromellose and titanium dioxide

10.2. Study Drug Packaging and Labeling

RTA 408 active and placebo capsules are contained in identical primary container closure systems (i.e., 75-cc high-density polyethylene bottles with a foil induction-seal liner and a child-resistant closure). Treatment kits containing up to six bottles, depending on treatment assignment, will be provided to patients for self-administration. Each bottle will contain 30 or 90 capsules and a desiccant insert that must not be ingested. The label on each bottle will include the following information:

- Protocol 408-C-1402
- Medication ID number
- Caution statement: New Drug – Limited by Federal Law to Investigational Use (United States [US])
- Storage: Controlled room temperature, 20°C to 25°C (68°C to 77°C), with excursions allowed between 15°C and 30°C (59°C to 86°C)
- Sponsor name, address, and contact information
- Contents: One bottle containing 30 capsules of either RTA 408 or matching placebo. Bottle also contains one desiccant insert, which should not be ingested
- Directions for use: Take capsule as directed, orally, once daily in the morning on an empty stomach (1 hour before or 2 hours after eating) with water
- Keep out of sight and reach of children
- FOR ORAL USE ONLY

Additionally, expiry information will be provided on treatment kits intended for use in the European Union (EU).

10.3. Study Drug Storage

The stability of the drug product is being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure location under controlled room temperature conditions of 20°C to 25°C (68°F to 77°F), with excursions allowed between 15°C and 30°C (59°F to 86°F). Sites must maintain a temperature log of the storage conditions. Temperature logs must be available for review at each monitor site visit. If a temperature within the storage location at the site is noted to be outside the excursion range for 24 hours or more or exceeds 40°C, the Sponsor must be notified.

10.4. Study Drug Administration

Please refer to Section 9.9.24 for details on study drug administration. Patients will receive enough capsules for continuous dosing once daily at least until the next study visit. Clear instructions will be provided to the patient regarding study drug administration for each study drug administration time point listed in Table 2, Table 3, and Table 4.

10.5. Study Drug Accountability

The investigator or designee will maintain a record of all study drug received, dispensed, and returned to the Sponsor or its designee. No study drug shall be destroyed by the clinical site unless directed to do so by the Sponsor or its designee. Study drug bottles and any unused capsules should be returned by the patient to the study staff.

10.6. Study Drug Handling and Disposal

At the conclusion of the study, the Sponsor or its designee will direct the site regarding the final disposition of any remaining study drug.

11. EFFICACY ASSESSMENTS

11.1. Part 1

11.1.1. Maximal Exercise Test

The changes in peak work and oxygen utilization during maximal exercise testing from Baseline to Weeks 4 and 12 will be analyzed.

11.1.2. Friedreich's Ataxia Rating Scale

The change in both the FARS neurological score and the mFARS scores from Baseline to Weeks 4, 8, and 12 will be analyzed.

11.1.3. 25-Foot Timed Walk Test

The change in 25-foot timed walk test distance from Baseline to Weeks 4, 8, and 12 will be analyzed.

11.1.4. Low-Contrast Letter Visual Acuity Test

The change in performance on the low-contrast letter visual acuity test from Baseline to Weeks 4, 8, and 12 will be analyzed.

11.1.5. 9-Hole Peg Test

The change in performance on the 9-HPT from Baseline to Weeks 4, 8, and 12 will be analyzed.

11.1.6. Fatigue Severity Scale

The change in Fatigue Severity Scale patient-reported outcome scores from Baseline to Week 12 will be analyzed.

11.1.7. SF-36 Health Survey Update

The change in SF-36 patient-reported outcome scores from Baseline to Week 12 will be analyzed.

[redacted]

11.2. Part 2

11.2.1. Friedreich's Ataxia Rating Scale

The change in both the FARS neurological score and the mFARS scores from Baseline to Weeks 4, 12, 18, 24, 36, and 48 will be analyzed.

11.2.2. Patient Global Impression of Change

The proportion of patients who are a treatment success at Weeks 12, 24, 36, and 48, based on the Patient Global Impression of Change. A treatment success is defined as "Much Improved" or "Very Much Improved" on the Patient Global Impression of Change.

11.2.3. Clinical Global Impression of Change

The proportion of patients who are a treatment success at Weeks 12, 24, 36, and 48, based on the Clinical Global Impression of Change. A treatment success is defined as "Much Improved" or "Very Much Improved" on the Clinical Global Impression of Change.

11.2.4. Maximal Exercise Test

The changes in peak work and oxygen utilization during maximal exercise testing from Baseline to Weeks 4, 12, 18, 24, 36, and 48 will be analyzed.

11.2.5. 9-Hole Peg Test

The change in performance on the 9-HPT from Baseline at Weeks 24 and 48 will be analyzed.

11.2.6. 25-Foot Timed Walk Test

The change in performance on the 25-foot timed walk test from Baseline at Weeks 24 and 48 will be analyzed

11.2.7. SF-36 Health Survey Update

The change in SF-36 patient-reported outcome scores from Baseline at Weeks 24 and 48 will be analyzed.

11.2.8. Activities of Daily Living

The change in ADL from Baseline at Weeks 24, 36, and 48 will be analyzed.

11.2.9. Frequency of Falls

The frequency of falls from Screening through Week 48 will be analyzed.

11.2.10. Distribution of Change in mFARS Scores

The proportion of patients at Week 48 with an mFARS change from baseline at or lower than specified cutoff values defined in the SAP (e.g., -2, -3, etc.) will be analyzed.

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

Safety parameters in Part 1 and Part 2 include results of echocardiogram, ECG, vital sign measurements, weight, BMI, physical examination, AEs, SAEs, concomitant medications, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-proBNP, and pregnancy tests [as indicated]). Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-proBNP, and pregnancy tests [as indicated]).

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Pre-planned elective procedures (surgeries or therapies) that are performed to manage/treat conditions that existed prior to the patient's enrolling in the trial (e.g., elective periodontal surgery, elective hernia repair) should not be recorded as AEs, but should be documented in the patient's source documents. If a pre-planned procedure is performed early (e.g., as an emergency) because the pre-existing condition worsens, the worsening condition should be captured as an AE.

All AEs that are observed or reported by the patient during the study (from the time of the first dose of study drug until the final visit or 30 days following final study dose for patients who terminate early) must be reported, regardless of their relationship to study drug or their clinical significance.

12.2.1.2. Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug

- Is an important medical event

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of first dose of study drug until the final visit). Certain pregnancy outcomes will require submission as an SAE (Section 9.7.3).

The investigator is responsible for reporting to the Sponsor or its designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of first dose of study drug until the final visit), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. The Sponsor or its designee may contact the investigator to obtain additional information on any SAE that has not resolved at the time the patient completes the study.

12.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, “How do you feel?” or “How have you been feeling since your last visit?” to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses should be recorded in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, ECG abnormalities, or other documents that are relevant to patient safety.

12.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

- Unrelated: This relationship suggests that there is no association between the study drug and the reported event.
- Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.
- Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from

the time of study drug administration and/or follows a known response pattern to the study drug but could have been produced by other factors.

- Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug administration seems likely.

12.5. Assessment of Severity

The investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

12.6. Recording Adverse Events

All conditions present prior to the first dose of study drug should be documented as medical history. All drug-related (characterized as possibly or probably related; Section 12.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs or non–drug-related abnormal laboratory results will be followed through the final visit (i.e., end of study or early termination). Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (e.g., worsening or improving) should be noted in the source documents but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF. AEs characterized as intermittent require documentation of onset and duration.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication (except disease progression) should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the

investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs but should be documented in the patient's source documents as elective (e.g., elective periodontal surgery). However, if a preplanned procedure is performed early (e.g., as an emergency) because of a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

12.7. Reporting Serious Adverse Events

Any AE that meets the criteria of serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event. For questions regarding SAE reporting, contact your study manager, monitor, or medical monitor.

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be reported.

The Sponsor is to notify all appropriate regulatory authorities, EudraVigilance Database, IRBs, and investigators of SAEs, as required by local law, within required time frames.

The Sponsor or its designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the time frame established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria but are reported to be associated with the use of the study drug (that is, "possible" or "probable" in causality assessment), the Sponsor or its designee will notify the appropriate regulatory agencies in writing within the time frame established by those regulatory agencies. The Sponsor or its designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for their information and submission to their IRB, as appropriate.

Principal investigators are responsible for informing their IRB of any SAEs at their site, as appropriate. The DSMB will review all safety data in an unblinded manner throughout the study and make recommendations as appropriate. SAE correspondence with regulatory authorities or IRBs must be submitted to the Sponsor or its designee for recording in the study file.

13. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

13.1. Pharmacokinetic Samples

PK samples will be analyzed for RTA 408 using a validated analytical method. Samples may be analyzed for potential metabolites of RTA 408 using non-validated analytical methods.

13.2. Pharmacodynamic Samples (Part 1 Only)

[redacted]

13.2.2. Platelet Analysis

Mitochondrial function and biochemical changes in metabolites of interest will be analyzed from platelet samples.

[redacted]

14. STATISTICS

14.1. Sample Size

Part 1:

The sample size for Part 1 is based on a dose-escalation scheme to evaluate initial safety, PK, and PD activity of RTA 408 in this patient population. The small number of patients at each dose in Part 1 is not expected to fully characterize safety, efficacy, or PD, but rather inform the DSMB and Sponsor of the appropriate doses to select for Part 2.

Part 2:

[redacted]

Extension:

The sample size for the extension is limited to the number of patients having completed Part 1 or Part 2.

14.2. Study Variables

14.2.1. Pharmacokinetic Variables

The PK variables include RTA 408 plasma concentration-time data and metabolite concentration-time data (if available), and relevant PK parameter values (e.g., C_{max}, T_{max}, AUC) for each analyte.

14.2.2. Pharmacodynamic Variables (Part 1 Only)

[redacted] platelet biomarkers, and [redacted]

14.2.3. Efficacy Variables

Part 1: Efficacy variables are peak work during maximal exercise testing, oxygen utilization during maximal exercise testing, mFARS scores, FARS score, 25-foot timed walk test distance,

9-HPT scores, low-contrast letter visual acuity test scores, Fatigue Severity Scale scores, and SF-36 scores.

Part 2: Efficacy variables are mFARS scores, full FARS scores, peak work during maximal exercise testing, parameters collected during maximal exercise testing (other than peak work), 9-HPT scores, 25-foot timed walk test distance, ADL, Patient Global Impression of Change, Clinical Global Impression of Change, and SF-36 scores.

14.2.4. Safety Variables

The safety variables in Part 1 and Part 2 include results of echocardiogram, ECGs, weight and BMI, vital sign measurements, physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis, microscopy, and pregnancy tests [as indicated]), concomitant medications, AEs, and SAEs. Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-proBNP, and pregnancy tests [as indicated]). All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and analyses of the AE data will be detailed in the SAP.

14.3. Statistical Analyses

Separate SAPs will be written for each study part. The SAPs will detail the analyses to be performed for each study part and will be developed prior to the database lock of each study part. The SAPs, which will describe in detail the methods used for the primary and secondary endpoints, will serve as the final arbiter of all statistical analyses.

Data will be summarized using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

14.3.1. Analysis Sets

Part 1 and Part 2 will be analyzed separately. For Part 1 and Part 2, the following analysis sets will be defined:

- The intent-to-treat (ITT) population includes all enrolled patients categorized by their assigned treatment group (whether or not they received study drug).
- The safety population includes all patients who received at least 1 dose of study drug. Patients who receive at least 1 dose of RTA 408 will be classified in the RTA 408 group at the highest dose level received.
- Additional analysis sets may be defined in the SAP as appropriate.

Extension: All patients who received at least 1 dose of study drug in the extension will be included in the extension safety population.

14.3.2. Primary Efficacy Analysis

Primary analysis of the efficacy data will be based on the ITT population. Mixed-model repeated measures (MMRM) analysis will be used to analyze the Part 1 and Part 2 primary and secondary

efficacy objectives. All scheduled efficacy values collected through the end of treatment visit (i.e., Week 12 in Part 1, Week 48 in Part 2) will contribute to the primary analysis. The primary analyses of efficacy with MMRM are expected to be at least as powerful as the 2-sided t-test calculations used for study planning.

The dependent variable will be change from baseline. The model may include treatment, visit, and the interaction between treatment and visit as fixed effects; and visit will serve as a repeated measure. The SAP will specify the choice of variance-covariance structure and may specify additional covariates. The SAP may specify additional covariates. Procedures for handling missing data and appropriate sensitivity analyses will be described in the SAP for each study part.

Extension analysis of safety: As the extension is of an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (i.e., RTA 408 or placebo).

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

The study monitor, as a representative of the Sponsor, has the obligation to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

The Sponsor or its designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6(R2), abbreviated as ICH E6(R2), and current standard operating procedures.

Each principal investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for study-related monitoring and to the internet during the visit.

15.2. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the US FDA, or other relevant regulatory authorities, access to all study records.

The principal investigator or designee should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its designee.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

16.2. Financial Disclosure

Principal investigators and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and sub-investigators must provide the Sponsor or its designee with updated information, if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Any potential investigator who has a vested financial interest in the success of this study may not participate in this study.

16.3. Sponsor Obligations

The Sponsor or its designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or its designee is not financially responsible for treatment of non–study-related fatalities, physical injuries, or damage to health that may occur during the clinical study, as well as the patient's underlying disease.

16.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R1), Section 8.2 and Title 21 of the US Code of Federal Regulations (CFR), abbreviated as US CFR Title 21, by providing the essential documents to the Sponsor or its designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol
- The IRB approval of the protocol
- The IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. A curriculum vitae and current licensure, as applicable, must be provided. The curriculum vitae must have been signed and dated by the principal investigators and sub-investigators within 2 years before study start-up to indicate the documents are accurate and current

- Completed financial disclosure forms (Section 16.2) to allow the Sponsor or its designee to submit complete and accurate certification or disclosure statements required under US CFR Title 21, Part 54. In addition, the investigators must provide to the Sponsor or its designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study
- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study

16.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential study-related fatalities, physical injuries, or damage to health that may occur during the clinical study.

16.6. Use of Information

All information regarding RTA 408 supplied by the Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of RTA 408 Capsules and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants, as required.

17. ETHICS

17.1. Institutional Review Board Review

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. Each site must provide the Sponsor or its designee a signed and dated statement that the protocol and ICF have been approved by the IRB before consenting patients. Prior to study initiation, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities, as required.

The IRB chairperson or designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The principal investigator must supply the Sponsor or its designee with written documentation of reviews of the clinical research.

17.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH E6(R1), with applicable local regulations (e.g., US CFR Title 21), the requirements of Clinical Trials Regulation (EU) No 536/2014, and with the ethical principles of the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the International Council for Harmonisation (ICH) for Guidance for Industry on GCP ICH E6(R1) [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

17.3. Written Informed Consent

Because the study will be conducted under a US Investigational New Drug Application, a signed ICF, in compliance with US CFR Title 21, Part 50, will be obtained from each patient before the patient enters the study. An informed consent template may be provided by the Sponsor or its designee to the investigators. The consent must be reviewed by the Sponsor or its designee before IRB submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all participants affected by the revision must sign the revised IRB-approved consent form in order to continue on the study.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent [FDA 1998]. Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the principal investigator or designee is assured that the patient understands the

implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB approval.

The principal investigator or designee will provide a copy of the ICF (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

17.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

The Sponsor will conduct this study, and process all personal data, according to the Sponsor policies related to data privacy, records retention and disposition, and information security. The Sponsor has developed, implemented, and will maintain a comprehensive, documented information security program that requires the implementation of administrative, physical, and technical safeguards to protect personal data against unauthorized or inappropriate use, access, or transmission. Such technical and organizational measures (including organizational processes and procedures) are designed to protect personal data from unauthorized use or access, accidental loss, damage, destruction, theft or disclosure, and to ensure that such measures are commensurate with the harm that may result from this. The Sponsor's information security controls are compliant with the National Institute of Standards and Technology Special Publication 800-53 (or the International Organization for Standardization equivalent) framework to protect the confidentiality of personal data.

17.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the principal investigator, and the IRB. In cases where the

protocol is modified to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB.

The principal investigator is responsible for informing the IRB of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify FDA in accord with US CFR Title 21, Part 312, Section 32.

17.6. Protocol Deviations

The principal investigator or designee must document any protocol deviations. The IRB must be notified of all protocol deviations in a timely manner by the investigator as appropriate. Protocol deviations will be documented by the site personnel and reviewed by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a patient, the principal investigator may deviate from the protocol without prior Sponsor and IRB approval. The Sponsor and IRB must be notified of the deviation.

18. DATA HANDLING AND RECORD KEEPING

18.1. Retention of Records

The investigator will maintain all study records according to ICH E6(R1) and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application is approved or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

In case of a suspected data security breach, the Sponsor will follow the procedure outlined in its data privacy and information security policies, which require immediate reporting to the Sponsor's Global Privacy Office so that risk and next steps (including reporting to data protection authorities and/or data subjects) can be assessed.

18.2. Case Report Forms

All data will be entered in electronic case report forms at the investigational site. The electronic data capture system used to capture data electronically for all patients who signed informed consent will be US CFR Title 21, Part 11 compliant.

19. PUBLICATION POLICY

The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. The Sponsor supports communication and publication of study results whatever the findings of the study. The Sponsor also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

Those individuals who have contributed greatly to this study, as determined by the Sponsor, may serve on any publications committee for the study.

In accordance with international standards, the results of the clinical trial will be reported within one year from the end of the clinical trial and duly substantiated reasons will be provided by the Sponsor if the submission of the summary of the results of the clinical trial is after more than one year.

Sponsor publications will be developed, reviewed, and approved in accordance with current good publications practice guidelines and industry standards (e.g., International Committee of Medical Journal Editors recommendations; Good Publication Practice guidelines; The International Federation of Pharmaceutical Manufacturers and Associations Position; The Consolidated Standards of Reporting Trials guidelines; the Pharmaceutical Research and Manufactures of America Principles) to ensure that the publications reflect accurate, balanced, timely, and transparent reporting and interpretation of research data.

20. LIST OF REFERENCES

D'Oria V, Petrini S, Travaglini L, et al. Frataxin deficiency leads to reduced expression and impaired translocation of NF-E2-related factor (Nrf2) in cultured motor neurons. Int J Mol Sci. 2013;14(4):7853-65. Epub 20130410.

Di Prospero NA, Baker A, Jeffries N, et al. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. Lancet Neurol. 2007;6(10):878-86.

Dürr A. Friedreich's ataxia: treatment within reach. Lancet Neurol. 2002;1(6):370-4.

FDA. Screening Tests Prior to Study Enrollment: Guidance for Institutional Review Boards and Clinical Investigators. Food and Drug Administration. Published 1998 [Accessed 01 Apr 2025]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment

Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976.

Holmström KM, Baird L, Zhang Y, et al. Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. Biol Open. 2013;2(8):761-70. Epub 20130620.

Honda T, Rounds BV, Bore L, et al. Novel synthetic oleanane triterpenoids: a series of highly active inhibitors of nitric oxide production in mouse macrophages. Bioorg Med Chem Lett. 1999;9(24):3429-34.

Jenkinson C, Stewart-Brown S, Petersen S, et al. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health. 1999;53(1):46-50.

Klockgether T, Lüdtke R, Kramer B, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain. 1998;121 (Pt 4):589-600.

Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology. 1989;46(10):1121-1123.

Liu J. Pharmacology of oleanolic acid and ursolic acid. J Ethnopharmacol. 1995;49(2):57-68.

Ludtmann MH, Angelova PR, Zhang Y, et al. Nrf2 affects the efficiency of mitochondrial fatty acid oxidation. Biochem J. 2014;457(3):415-24.

Marmolino D. Friedreich's ataxia: past, present and future. Brain Res Rev. 2011;67(1-2):311-30. Epub 20110417.

Neymotin A, Calingasan NY, Wille E, et al. Neuroprotective effect of Nrf2/ARE activators, CDDO ethylamide and CDDO trifluoroethylamide, in a mouse model of amyotrophic lateral sclerosis. Free Radic Biol Med. 2011;51(1):88-96. Epub 20110330.

Paupe V, Dassa EP, Goncalves S, et al. Impaired nuclear Nrf2 translocation undermines the oxidative stress response in Friedreich ataxia. PLoS One. 2009;4(1):e4253. Epub 20090122.

Saha PK, Reddy VT, Konopleva M, et al. The triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic-acid methyl ester has potent anti-diabetic effects in diet-induced diabetic mice and Lepr(db/db) mice. J Biol Chem. 2010;285(52):40581-92. Epub 20101018.

Shin S, Wakabayashi J, Yates MS, et al. Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-imidazolide. Eur J Pharmacol. 2009;620(1-3):138-44. Epub 20090819.

Uruno A, Furusawa Y, Yagishita Y, et al. The Keap1-Nrf2 system prevents onset of diabetes mellitus. Mol Cell Biol. 2013;33(15):2996-3010. Epub 20130528.

21. APPENDICES

APPENDIX 1. EXTENSION ELIGIBILITY CRITERIA

Extension Inclusion Criteria

Patients must:

1. Have adequate kidney function defined as an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) 4-variable formula
2. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
3. Be able to swallow capsules
4. Be willing and able to cooperate with all aspects of the extension
5. Be willing to practice medically acceptable methods of birth control (Section 9.7.2)
6. Provide written informed consent for study participation, approved by the appropriate Institutional Review Board (IRB)
7. Have been enrolled in Part 1 or Part 2 and completed assessments through the follow-up visit with no major protocol deviations that would, in the opinion of the investigator, deem the patient unsuitable for enrollment in the extension phase of the study.

Extension Exclusion Criteria

Patients must not:

1. Have uncontrolled diabetes (HbA1c > 11.0%)
2. Have B-type natriuretic peptide (BNP) level > 200 pg/mL
3. Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease
    b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
    c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
    d. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
    e. History of hospitalization for heart failure in the last five years
    f. Cardiac insufficiency, defined as New York Heart Association Class > 2
    g. History of atrial fibrillation
    h. History of unstable arrhythmias

4. Have known active fungal, bacterial, and/or viral infection, including human immunodeficiency virus (HIV) or hepatitis virus (B or C)
5. Have known or suspected active drug or alcohol abuse, as per investigator judgment
6. Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal of AST or ALT. Levels above this threshold are allowable if attributable to muscle injury
7. Have any abnormal laboratory test value or clinically significant pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by study enrollment
8. Have taken any of the following drugs within 7 days prior to Extension Day 1 or plan to take any of these drugs during the time of study participation:
    a. Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)
    b. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)
    c. Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)
9. Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, at screening, clinically relevant deviations in laboratory tests including any one of the following:
    a. alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 1.5-fold ULN,
    b. bilirubin > 1.2-fold ULN,
    c. alkaline phosphatase (ALP) > 2-fold ULN,
    d. albumin < lower limit of normal (LLN)
10. Have participated in any other interventional clinical study within 30 days prior to Extension Day 1
11. Have a cognitive impairment that may preclude ability to comply with study procedures
12. Be unable to comply with the requirements of the study protocol or be unsuitable for the study for any reason, in the opinion of the investigator
13. Have a history of thromboembolic events within the past 5 years
14. Have taken anticoagulant therapy within 30 days prior to Extension Day 1
15. Have had significant current suicidal ideation within 1 month prior to Extension Day 1 as per investigator judgment or any history of suicide attempts
16. Be pregnant or breastfeeding
17. Have an ongoing SAE from a clinical study that is assessed by the investigator as related to RTA 408
18. Have discontinued treatment early in Part 1 or Part 2.

APPENDIX 2. MAXIMAL EXERCISE TEST

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Maximal Exercise Test

Source Document

Visit Date (dd/MMM/yyyy): __ __/__ __ __/__ __ __ __

Was Maximal Exercise Test performed?	☐ Yes ☐ No
If no, specify reason: ☐ Not Applicable	
Height:	_____ in. OR _____ cm
Weight:	_____ . _____pounds OR _____ kilograms
Resting Data (record measurements while subject is at rest in supine position)	
Start Time:	_____ : _____
Was resting ECG collected?	☐ Yes → Print ECG data for source ☐ No → Specify: _____ _____
Heart Rate	_____beats/min
Oxygen saturation by pulse oximeter (SpO2)	_____%
Resting Blood Pressure	Systolic Reading : _____mm Hg Diastolic Reading: _____mm Hg
Resting minute oxygen consumption (VO2)	_____L/min
Resting Pulmonary Function Performed via Spirometry (Please capture data by hand if it is not captured electronically by metabolic cart)	
Forced Vital Capacity (FVC)	_____L
Forced expiration volume with one second (FEV)	_____L
Maximum voluntary ventilation (MVV)	_____L/min
Predicted Forced Vital Capacity	_____%
Warm-up	
Warm-up Start Time:	_____ : _____
Was patient able to maintain 65-75 rpm at no resistance?	☐ Yes ☐ No
BORG in warm-up	_____

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Maximal Exercise Test

Source Document

Active Exercise Test Ramp Protocol to be followed – check watt and time increases at each time point patient is ramped up. Please note, you may not use all time points below or may need additional time points to capture the full test. If additional time points are needed to capture the full test, please use the "Active Exercise Test – continuation page".		
Start Time:		_____ : _____
1.	Initial Watt Increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
2.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
3.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
4.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
5.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
6.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
7.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
Reason for end of test:		☐ Patient is unable to complete due to: ☐ spasticity ☐ other→ Specify:_____ ☐ Inability to maintain rpm speed
Max Watt at Exhaustion:		_____ W
BORG at end of test:		_____

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Maximal Exercise Test

Source Document

End Time:	_____ : _____
Total time to complete test:	_____min
Exercise Peak Performance Measurements	
Max VO2 (Please record both values)	_____ L/min _____ ml/kg/min
VCO2	_____ L/min
Anaerobic Threshold	_____ L/min
Maximum Work Load	_____ Watts
Length of time to reach maximal work	_____ min(s) : _____ sec(s)
Maximum rating of perceived exertion (BORG)	_____
Maximum Heart Rate	_____ beats/min
Maximum Blood Pressure	Systolic Reading: _____ mm Hg Diastolic Reading: _____ mm Hg
Oxygen saturation by pulse oximeter (SpO2)	_____ %
Respiratory Quotient	_____
Peak Exercise Ventilatory response measurements	
Maximum Minute Ventilation (VE) BTPS	_____ L/min
Tidal Volume	_____ L
Maximum Respiratory Rate	_____ breaths/min
Breathing Reserve	_____ %
2 Minute Recovery	
Did patient complete 2 minute recovery?	☐ Yes ☐ No
BORG at end of 2 minutes:	_____
RER at 1.5 minutes of recovery	_____
10 Minute Observation	
Did patient's blood pressure return to adequate baseline levels?	☐ Yes ☐ No
Recovery Blood Pressure:	Systolic Reading : _____mm Hg Diastolic Reading: _____mm Hg
Time for BP to return to adequate baseline levels?	_____min
Did patient's heart rate return to adequate baseline levels?	☐ Yes ☐ No

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Maximal Exercise Test

Source Document

Recovery Heart Rate:	_____beats/min
Time for heart rate to return to adequate baseline levels?	_____min

Assessor's Signature: _____ Date (dd/MMM/yyyy): __ __/ __ __ __/ __ __ __ __

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Maximal Exercise Test

Source Document

Active Exercise Test – Continuation page Ramp Protocol to be followed – check watt and time increases at each time point patient is ramped up. Please note, you may not use all time points below or may need additional time points to capture the full test. If additional time points are needed to capture the full test, site can make multiple copies of this page.		
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____
___.	Time increment to next increase	☐ 1 min ☐ 2 min
	Watt increase	☐ 5W ☐ 6W ☐ 7W ☐ 8W ☐ 9W ☐ 10W ☐ Other, Specify: _____
	BORG at increase	_____

APPENDIX 3. FARS ASSESSMENT

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Neurological FARS

Source Document

Visit Date (dd/MMM/yyyy): __ __/__ __ __/__ __ __ __

NEUROLOGICAL EXAMINATION *Neurologist to conduct exam. *If there are any questions on how to complete the exam, please refer to the FA Study Manual provided. *Rate each item on the basis of the subject status during examination. To the extent possible, sequential subject examinations should be carried out at the same time of day.	
A. BULBAR Most subjects with FA do not have significant facial or tongue atrophy. If mild facial or tongue atrophy is noted score as per instructions. Speech and cough assessment is self-explanatory. For items in Section A, increments of 0.5 may be used if examiner feels an item falls between two severities.	
1. Facial Atrophy, Fasciculation, Action Myoclonus, and Weakness 0 – None 1 – Fasciculations or action myoclonus, but no atropy. 2 – Atrophy present but not profound of complete. 3 – Profound atrophy and weakness.	Score ☐.☐
2. Tongue Atrophy, Fasciculation, Action Myoclonus, and Weakness 0 – None 1 – Fasciculations or action myoclonus, but no atropy. 2 – Atrophy present but not profound of complete. 3 – Profound atrophy and weakness.	Score ☐.☐
3. Cough (subject asked to cough forcefully 3 times) 0 – Normal. 1 – Depressed. 2 – Totally or nearly absent.	Score ☐.☐
4. Speech (ask the patient to read or repeat the sentences: A. "The president lives in the white house" and B. "The traffic is heavy today") 0 – Normal. 1 – Mild (all or most words understandable). 2 – Moderate (most words not understandable). 3 – Severe (no or almost no useful speech).	Score ☐.☐
TOTAL BULBAR SCORE:	☐☐.☐

Site ID: __ __ __ __ Patient ID: __ __ __ __ __ __ __ Patient Initials: __ __ __

Protocol 408-C-1402-Part 2

Week 48 Visit: Neurological FARS

Source Document

B. UPPER LIMB COORDINATION

Upper limb coordination: Most of the items are self-explanatory. For items 3-5, ask the subject to count as they do the task.

Example: "Move your hand back and forth 10 times as fast as you can. Please count each time to yourself".

You can time the activity with either a watch or a stopwatch. For items in Section B, increments of 0.5 may be used if examiner feels an item falls between two severities.

1. **Finger to Finger Test** (Index fingers are placed in front of each other with flexion at the elbow about 25 cm. from the sternum. Observe for 10 seconds. Score amplitude of oscillations) 0 – Normal. 1 – Mild oscillations of finger (less than 2 cm). 2 – Moderate oscillations of finger (2-6 cm). 3 – Severe oscillations of finger (greater than 6 cm)	Score (Right) ☐.☐ Score (Left) ☐.☐
2. **Nose-Finger Test** (Assess kinetic or intention tremor during and towards the end of movement: examiner holds index finger at 90% reach of patient; test at least 3 nose-finger-nose trials; movement slow greater than 3 sec.) 0 - None 1 - Mild (less than 2 cm. amplitude). 2 - Moderate (2-6 cm. amplitude or persisting through movement). 3 - Severe (greater than 6 cm. & persisting through movement). 4 - Too poorly coordinated to perform task.	Score (Right) ☐.☐ Score (Left) ☐.☐
3. **Dysmetria Test** (The subject touches tip of examiner's finger then subject's chin 8 times as rapidly as possible while the examiner moves his finger to four corners of a one foot square and at about 90% reach of the subject. Assess dysmetria – i.e. inaccuracy of reaching the target- tip of examiner's finger) 0 - None. 1 - Mild (misses 2 or fewer times). 2 - Moderate (misses 3-5 times). 3 - Severe (misses 6-8 times.). 4 - Too poorly coordinated to perform task.	Score (Right) ☐.☐ Score (Left) ☐.☐
4. **Rapid Alternating Movements of Hands** (Subject should be seated. Forearm pronation/supination 15 cm. above thigh; 10 full cycles as fast as possible; assess rate, rhythm, accuracy; practice 10 cycles before rating, if time greater than 7 sec. add 0.5 to score. Use stopwatch) 0 - Normal. 1 - Mild (slightly irregular or slowed). 2 - Moderate (irregular and slowed). 3 – Too poorly coordinated to perform task. Time to Complete (R): _____ Time to Complete (L): _____	Score (Right) ☐.☐ Score (Left) ☐.☐

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5. **Finger Taps** (index fingertip-to-thumb crease; 15 reps as fast as possible; practice 15 reps once before rating; if time greater than 6 sec., add 1 to rating. Use stopwatch) 0 - Normal. 1 - Mild (misses 1-3 times). 2 - Moderate (misses 4-9 times). 3 - Severe (misses 10-15 times). 4 - Cannot perform the task. Time to complete (R): _____ Time to complete (L): _____	Score (Right) ☐☐.☐ Score (Left) ☐☐.☐
TOTAL UPPER LIMB COORDINATION SCORE	☐☐.☐
C. LOWER LIMB COORDINATION Lower limb coordination: The heel shin slide is scored 1 if there is an abnormality but contact is steady along the top of the shin. If the heel starts going off the shin to one or other side score 2 or 3 as noted. For heel to shin tap instruct the subject to count 8 taps with heel raised about 8 " each time. It is preferable to do this section with the patient lying down. If this is not followed for a particular subject, it should be done in the same position each time. For items in Section C, increments of 0.5 may be used if examiner feels an item falls between two severities.	
1. **Heel Along Shin Slide** (Perform while seated or supine, under visual control, slide heel on the contralateral tibia from the patella to the ankle up and down with contralateral leg extended, 3 cycles at moderate speed, one leg at a time.) 0 - Normal (stay on shin). 1 - Mild (abnormally slow, tremulous but contact maintained). 2 - Moderate (goes off shin a total of 3 or fewer times during 3 cycles). 3 - Severe (goes off shin 4 or more times during 3 cycles). 4 - Too poorly coordinated to attempt the task. Position of patient:_____	Score (Right) ☐☐.☐ Score (Left) ☐☐.☐
2. **Heel-to-Shin Tap** (Subject taps heel on midpoint of opposite shin 8 times on each side from about 6-10", one at a time. Perform seated or supine.) 0 - Normal (stays on target). 1 - Mild (misses shin 2 or <less times). 2- Moderate (misses shin 3-5 times). 3 - Severe (misses shin greater than times). 4 - Too poorly coordinated to perform task. Position of patient:_____	Score (Right) ☐☐.☐ Score (Left) ☐☐.☐
TOTAL LOWER LIMB COORDINATION SCORE	☐☐.☐

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D. PERIPHERAL NERVOUS SYSTEM

Peripheral nervous system: these items are self-explanatory. Check deltoids and intrinsic hand muscles in the upper limbs, iliopsoas and tibialis anterior in the lower limbs. Atrophy and weakness are scored on the basis of the worst muscle in this group. One does not have to do extensive muscle testing. Vibration sense is recorded as noted in seconds and then given a score depending on the extent of impairment. DTR are recorded in the given space as noted and then any hypo/areflexia is given a numerical score as noted.

1. Muscle Atrophy (score most severe atrophy in either upper or lower limb) 0 - None. 1 - Present - mild/moderate 2 - Severe/total wasting If atrophy is present or severe, indicate location of atrophy (R):_____ If atrophy is present or severe, indicate location of atrophy (L):_____	Score (Right) ☐ Score (Left) ☐
2. Muscle Weakness (Test deltoids, interossei, iliopsoas and tibialis anterior. Score most severe weakness in either upper or lower limb) 0 - Normal (5/5). 1 - Mild (movement against resistance but not full power 4/5). 2 - Moderate (movement against gravity but not with added resistance 3/5) 3 - Severe (movement of joint but not against gravity 2/5). 4 - Near paralysis (muscular activity without movement 1/5) 5 - Total paralysis (0/5)	Score (Right) ☐ Score (Left) ☐
3. Vibratory Sense (Educate patient regarding the sensation at the elbow. Tested with 128 cps tuning fork set to near full vibration; eyes closed; test over index finger and top of great toe (most distal joint not nail). Abnormal less than 15 seconds for toes and less than 25 seconds for hands) 3a. Time felt for toes (R): _____ 3b. Time felt for toes (L): _____ 3c. Time felt for Fingers (R): _____ 3d. Time felt for Fingers (L): _____ 3e. RIGHT 0 - Normal. 1 - Impaired at toes or fingers. 2 - Impaired at toes and fingers. 3e. LEFT 0 - Normal. 1 - Impaired at toes or fingers 2 - Impaired at toes and fingers.	Score (Right) ☐ Score (Left) ☐
4. Position Sense (test using minimal random movement of distal interphalangeal joints of index finger and big toe) 0 - Normal. 1 - Impaired at toes or fingers. 2 - Impaired at toes and fingers.	Score (Right) ☐ Score (Left) ☐

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5. DTR (0 = absent, 1 = hyporeflexia, 2 = normal, 3 = hyperreflexia, 4 = pathologic hyperreflexia) 5a. RIGHT / 5b. LEFT Elbow (BJ): _____ Elbow (BJ): _____ Wrist (BrJ): _____ Wrist (BrJ): _____ Knee (KJ): _____ Knee (KJ): _____ Ankle (AJ): _____ Ankle (AJ): _____ 5c. RIGHT 0 – No areflexia. 1 – Areflexia or mild hyperreflexia in either upper of lower limbs. 2 – Generalized areflexia or pathologic hyperreflexia. 5c. LEFT 0 – No areflexia. 1 – Areflexia or mild hyperreflexia in either upper of lower limbs. 2 – Generalized areflexia or pathologic hyperreflexia.	Score (Right) ☐☐ Score (Left) ☐☐
TOTAL PERIPHERAL NERVOUS SYSTEM SCORE	☐☐

E. UPRIGHT STABILITY

For sitting posture patient can sit in a chair or examination table. For standing and walking assessment instruct patient to wear best walking shoes and record below if barefoot, footwear or AFOs used. Stance assessment begins with feet 20 cm apart. Place marker tapes in the exam room 20 cm apart and the insides of the feet are lined up against these. Subsequent stance tests get more difficult. For feet together the entire inside of the feet should be close together as much as possible. For tandem stance, the dominant foot is in the back and the heel of the other foot is lined with the toes of the dominant foot but not in front of the toes (because this makes it even more difficult). For one foot stance, the patient is asked to stand on dominant foot and the other leg is elevated by bringing it forward with knee extended; this gives some advantage to the patient. If a patient can stand in a particular position for 1 minute or longer in trial 1, the trials 2 and 3 are abandoned. Otherwise each of 3 trials is timed and then averaged. Grading scores are then given as noted. Tandem walk and gait are performed in a hallway. Preferably no carpet but at least serial examinations should be on the same surface. For gait place markers 25 feet apart. Patient walks the distance turns around and comes back and the activity is timed. Note if the gait was achieved with or without device and serial examinations should be done with the same device as in the first examination.

Ea. Is subject:
☐ Barefoot ☐ Footwear

Eb. Indicate if AFO's (plastic brace) are used?
☐ No
☐ Yes

Ec. Test performed on Carpet?
☐ No
☐ Yes

1. Sitting Posture (Subject seated in chair with thighs together, arms folded across chest, back unsupported; observe for 30 sec.) 0 - Normal. 1 - Mild oscillations of head/trunk without touching chair back or side. 2 - Moderate oscillations of head/trunk; needs contact with chair back or side for stability.	Score ☐

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3 - Severe oscillations of head/trunk; needs contact with chair back or side for stability. 4 - Support on all 4 sides for stability.	
2a. Stance - feet apart – Eyes open (Inside of feet 20 cm apart marked on floor. Use stopwatch; 3 attempts; time in seconds. If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐ Avg. Score ☐.☐
2b. Stance - feet apart – Eyes closed (if greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐ Avg. Score ☐.☐
3a. Stance - feet together – Eyes open (use stopwatch; 3 attempts; time in seconds. If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐ Avg. Score ☐.☐
3b. Stance - feet together – Eyes closed (If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐

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	Avg. Score ☐.☐
4. Tandem Stance (dominant foot in front; front foot lined up with great toe of the back foot. If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐ Avg. Score ☐.☐
5. Stance on Dominant Foot (elevate leg straight out in front, use stopwatch; 3 attempts; time in seconds. If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials.) 0 - 1 minute or longer. Time 1: _____ 1 – less than 1 minute, greater than 45 sec. 2 – less than 45 sec., greater than 30 sec. Time 2: _____ 3 – less than 30 sec., greater than 15 sec. 4 – less than 15 sec. or needs hands held by assistant/device. Time 3: _____	Score 1 ☐ Score 2 ☐ Score 3 ☐ Avg. Score ☐.☐
6. Tandem Walk (tandem walk 10 steps in straight line; performed in hallway with no furniture within reach of 1 m / 3 ft. and no loose carpet) 0 - Normal (able to tandem walk greater than 8 sequential steps). 1 - Able to tandem walk in less than perfect manner/can tandem walk greater than 4 sequential steps, but less than 8. 2 - Can tandem walk, but fewer than 4 steps before losing balance. 3 - Too poorly coordinated to attempt task.	Score ☐
7. Gait (observe subject walk at normal pace with assistive device in one direction, turn around and return to start; performed in hallway with no furniture within reach of 1 m / 3 ft. and no loose carpet) 0 - Normal. 1 - Mild ataxia/veering/difficulty in turning; no cane/other support needed to be safe. 2 - Walks with definite ataxia; may need intermittent support/or examiner needs to walk with patient for safety sake.	Score ☐

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3 - Moderate ataxia/veering/difficulty in turning; walking requires cane/holding onto examiner with one hand to be safe. 4 - Severe ataxia/veering; walker or both hands of examiner needed. 5 - Cannot walk even with assistance (wheelchair bound).	
TOTAL UPRIGHT STABILITY SCORE	☐☐.☐
TOTAL FARS (Add subtotals for sections A, B, C, D, & E)	☐☐☐.☐
MODIFIED FARS (Total FARS – Section D)	☐☐☐.☐

Assessor's Signature: _____ Date (dd/MMM/yyyy): __ __/ __ __ __/ __ __ __ __

APPENDIX 4. 9-HOLE PEG TEST

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. Both the dominant and non-dominant hands are tested twice (2 consecutive trials of the dominant hand, followed immediately by 2 consecutive trials of the non-dominant hand). It is important that the 9-HPT be administered on a solid table (not a rolling hospital bedside table) and that the 9-HPT apparatus be anchored (e.g., with Dycem). Instructions on completing the 9-HPT are provided in the study manual.

APPENDIX 5. SF-36 HEALTH SURVEY UPDATE

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX 6. ACTIVITIES OF DAILY LIVING

II. ACTIVITIES OF DAILY LIVING (increments of 0.5 may be used if strongly felt that a task falls between 2 scores)

1. Speech ☐

0 - Normal
1 - Mildly affected. No difficulty being understood.
2 - Moderately affected. Sometimes asked to repeat statements.
3 - Severely affected. Frequently asked to repeat statements.
4 - Unintelligible most of the time.

2. Swallowing ☐

0 - Normal.
1 - Rare choking (< once a month).
2 - Frequent choking (< once a week, > once a month).
3 - Requires modified food or chokes multiple times a week. Or patient avoids certain foods.
4 - Requires NG tube or gastrostomy feedings.

3. Cutting Food and Handling Utensils ☐

0 - Normal.
1 - Somewhat slow and clumsy, but no help needed.
2 - Clumsy and slow, but can cut most foods with some help needed. Or needs assistance when in a hurry.
3 - Food must be cut by someone, but can still feed self slowly.
4 - Needs to be fed.

4. Dressing ☐

0 - Normal.
1 - Somewhat slow, but no help needed.
2 - Occasional assistance with buttoning, getting arms in sleeves, etc. or has to modify activity in some way (e.g. Having to sit to get dressed; use velcro for shoes, stop wearing ties, etc.).
3 - Considerable help required, but can do some things alone.
4 - Helpless.

5. Personal Hygiene ☐

0 - Normal.
1 - Somewhat slow, but no help needed.
2 - Very slow hygienic care or has need for devices such as special grab bars, tub bench, shower chair, etc.
3 - Requires personal help with washing, brushing teeth, combing hair or using toilet.
4 - Fully dependent

6. Falling (assistive device = score 3)

0 - Normal.
1 - Rare falling (< once a month).
2 - Occasional falls (once a week to once a month).
3 - Falls multiple times a week or requires device to prevent falls.
4 - Unable to stand or walk.

☐

7. Walking (assistive device = score 3)

0 - Normal.
1 - Mild difficulty, perception of imbalance.
2 - Moderate difficulty, but requires little or no assistance.
3 - Severe disturbance of walking, requires assistance or walking aids.
4 - Cannot walk at all even with assistance (wheelchair bound).

☐

8. Quality of Sitting Position

0 - Normal.
1 - Slight imbalance of the trunk, but needs no back support.
2 - Unable to sit without back support.
3 - Can sit only with extensive support (Geriatric chair, posy, etc.).
4 - Unable to sit.

☐

9. Bladder Function (if using drugs for bladder, automatic score of 3)

0 - Normal.
1 - Mild urinary hesitance, urgency or retention (< once a month).
2 - Moderate hesitance, urgency, rare retention/incontinence (> once a month, but < once a week).
3 - Frequent urinary incontinence (> once a week).
4 - Loss of bladder function requiring intermittent catheterization/indwelling catheter.

☐

TOTAL ACTIVITIES OF DAILY LIVING SCORE: ☐

APPENDIX 7. PATIENT GLOBAL IMPRESSION OF CHANGE

The Patient Global Impression of Change is a 7-point scale that requires patients to assess how much their illness has improved or worsened relative to their baseline state at the beginning of the trial. Patients will self-rate their perceived change by completing the following statement: "Since I began trial treatment, my overall status is:"

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

APPENDIX 8. CLINICAL GLOBAL IMPRESSION OF CHANGE

The Clinical Global Impression of Change is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention [Guy 1976]. The Clinician Global Impression of Change is assessed by completing the following statement “Compared to the patient’s condition at the start of the trial, this patient’s overall status is…”

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

APPENDIX 9. LOW-CONTRAST LETTER VISUAL ACUITY TEST (PART 1 ONLY)

Due to the frequency of visual deficits in Friedreich's ataxia, assessment of visual function plays an important role in clinical trials and clinical practice. Vision testing is done using a portable retro-illuminated vision board. A pre-measured yellow vision string (full length is 3.2 meters, red mark denotes 2 meters) is used to measure the distance from the patient's forehead to the vision board. A pointer is also used to orient the patient to the specific line they are being asked to read.

Additional details regarding administration of the low-contrast visual acuity test will be provided in a study specific manual.

APPENDIX 10. FATIGUE SEVERITY SCALE (PART 1 ONLY)

Fatigue Severity Scale (FSS, English version)*

	strongly disagree ◄ 1	2	3	4	5	6	► *strongly agree* 7
1. My motivation is lower when I am fatigued.	0	0	0	0	0	0	0
2. Exercise brings on my fatigue.	0	0	0	0	0	0	0
3. I am easily fatigued.	0	0	0	0	0	0	0
4. Fatigue interferes with my physical functioning.	0	0	0	0	0	0	0
5. Fatigue causes frequent problems for me.	0	0	0	0	0	0	0
6. My fatigue prevents sustained physical functioning.	0	0	0	0	0	0	0
7. Fatigue interferes with carrying out certain duties and responsibilities.	0	0	0	0	0	0	0
8. Fatigue is among my three most disabling symptoms.	0	0	0	0	0	0	0
9. Fatigue interferes with my work, family, or social life.	0	0	0	0	0	0	0

**Patients are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicates strongly disagree and 7, strongly agree.* [Krupp et al, Arch Neurol 1989]

[redacted]

[redacted]

APPENDIX 13. COVID-19 MITIGATIONS

This appendix outlines the mitigation strategies adopted to protect the health of participants in Study 408-C-1402, while maintaining compliance with good clinical practice (GCP) and minimizing the risk to trial integrity during the COVID-19 (Coronavirus Disease 2019) pandemic. At the time of the pandemic, Parts 1 and 2 of Study 408-C-1402 were already completed, therefore, this appendix applies to the extension phase of the study.

The mitigations specified below will be in place as long as COVID-19 related local government restrictions impact trial conduct, according to protocol specifications.

1. SITE OPERATIONS & PATIENT MANAGEMENT

If study sites are closed or restrict access to study teams during the COVID-19 pandemic, study teams must maintain open lines of communication with active study participants. Additionally, the Sponsor is to be regularly updated on changes to sites' status regarding closures, access limitations, contact information or other important information. Sites are encouraged to provide alternate contact information to their patients and the Sponsor. Updates are to be sent to the Sponsor study team.

2. COVID-19 TESTING AND INVESTIGATIONAL PRODUCT USE

If a patient enrolled in the extension phase of Study 408-C-1402 tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the investigational product (IP) RTA-408 (omaveloxolone) must be temporarily discontinued until the patient no longer presents an active infection, defined as resolution of symptoms or a negative test, as assessed by the Investigator and/or the patient's physician(s). The Sponsor must be notified immediately for additional guidance.

2.1. Resumption of Investigational Product after Recovery from COVID-19 Infection

The duration of treatment interruption due to COVID-19 infection must be determined based on the patient's symptoms and the investigator's discretion. Patients who interrupt treatment for no more than 14 days may resume study drug without an in-person visit, at the investigator's discretion, if COVID-19 symptoms have resolved or a negative test is presented.

If the duration of treatment interruption exceeds 14 days and the investigator deems that the patient can safely complete an in-person visit, the investigator should conduct an unscheduled visit and perform all assessments as in Week 4. If there are no changes in clinical status that would preclude resuming IP, IP may be resumed. A follow-up telephone visit should be conducted approximately 2 weeks after this unscheduled visit to collect adverse events and prior and concomitant medications. Approximately four weeks after the unscheduled visit, the patient should return for repeat assessments as in the Week 4 visit. The usual visit schedule may resume thereafter. If an in-clinic visit is not possible, visits can be conducted as a combination of a telephone visit and a home health nurse visit.

3. INVESTIGATIONAL PRODUCT (IP) ACCESS

In order to maintain dosing continuity during the COVID-19 pandemic, IP may be directly shipped to the patient, using couriered tracking services, in cases where the patient becomes unable to travel to his/her study site. All shipments must be sent via overnight express shipping (where possible). Shipments should include a temperature monitoring device if required based on

sponsor guidance. Sites will be supplied with temperature monitors upon request. For shipments that show temperature excursions below 20°C or above 25°C during transit, the Sponsor should be notified immediately via the COVID-19 Investigational Product Temperature Excursion form. The Sponsor will assess whether the product is deemed fit for use. During the assessment period, the patient should be informed to not take the IP until further notice from the site. IP dispensation should be recorded in the appropriate drug accountability logs and all IP receipts of delivery should be filed in the Investigative Site File. If a patient is located in a country different from that of the site, the site will also provide information for customs on the shipped package.

4. STUDY VISIT

Where in-person clinic visits are not possible, in-home visits and/or telemedicine visits (e.g., phone or video) may be conducted to complete study assessments not limited to:

- Adverse event assessment.
- Prior and concomitant medication assessment.
- Pregnancy testing for women of childbearing potential (WOCBP): patients must complete scheduled urine pregnancy tests at home. Pregnancy test(s) should be provided to patients where relevant. The site should obtain verbal confirmation from the patients that the test is negative prior to instructing the patients to start the shipped RTA-408 IP. Additionally, the site will specifically remind patients of the need to adhere to appropriate protocol required contraceptive measures where necessary.
- Vital signs.
- Safety labs: Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator.

4.1. United Kingdom Site

Per regulatory authority requirements, every effort should be made to obtain safety laboratory assessments every 24 weeks (Table 4) using either the central laboratory, local laboratories, or home health services (if available). In cases when laboratory assessments cannot be performed as a result of COVID-19 related restrictions, alternative proportionate mechanisms of oversight should be followed to ensure patient safety and well-being.

Specifically, alternative mechanisms of oversight to liver function and BNP tests were employed based on benefit-risk assessment in the context of the guidance for Investigators provided in the Investigator's Brochure.

For the six-monthly visits, the following alternative proportionate oversight approach should be followed:

- Telephone Questionnaire

  Hepatic questions

  – Have you noticed any yellowing of your skin or eyes?
  – Have you noticed any usual swelling of your abdomen or feet?
  – Are you bruising very easily or had any cuts that kept bleeding?

  - Has your skin become itchy?
  - Have you had any changes in the color of your urine or stool?
  - Have you had any pain in the right upper quadrant of your abdomen?
  - Have you felt particularly nauseous?

  Fluid overload/Cardiac questions

  - Have you had any pain in your chest?
  - Have you become more short of breath?
  - Can you lie flat in bed without getting short of breath?
  - Have you noticed your heart racing or going into a funny rhythm?
  - Have you felt like you are going to faint? Or fainted?
- Additional hepatic recommendations
  - Continue site education regarding concomitant medication, particularly medications and/or supplements that are associated with hepatic injury including paracetamol.
  - Include urine bilirubin (if possible) with home urine dipstick.
- Home weight for fluid overload/cardiac assessments
  - Weight gain will be used to monitor fluid status.
  - Last home weight is used as baseline.
  - Patient(s) who experience a five-pound (2.3 kilograms) or greater increase in weight compared to the last home weight will be instructed to contact the site to assess the need to hold RTA-408 IP by the Investigator. IP should be discontinued if clinically important fluid retention is suspected.

Importantly, the alternative proportionate oversight measures outlined above can only be used for a certain period before safety laboratory assessments must be collected to conclusively measure relevant safety parameters. The maximum medically accepted delay in performing laboratory assessments (either local or on study) is 12 weeks post a six-monthly visit, assuming alternative proportionate oversight is ongoing and no concerns arise from this oversight.

If safety laboratory assessments cannot be completed within the maximum medically accepted delay, study drug must be temporarily discontinued until safety laboratory assessments can be obtained and it is deemed appropriate to restart IP dosing.

Biogen US Corporation
225 Binney Street
Cambridge, MA 02142
United States

Reata Pharmaceuticals, Inc.
225 Binney Street
Cambridge, MA 02142
United States

AMENDMENT SUMMARY

Biogen Protocol 408-C-1402

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia

Version 14.0

Date: 21 April 2025

US IND Number: 122349

EU CT Number: 2024-517436-22

Version 14.0 of the protocol has been prepared for this amendment, which supersedes Version 13.0.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 408-C-1402 is to make updates to ensure the protocol is aligned with the EU CTR No 536/2014 requirements for protocols.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 5.1, Background and Rationale for RTA 408 in Friedreich's Ataxia

Change: Section was updated to indicate whether patients with the disease of interest were involved in the design of the study.

Now reads:

…

Patients with the disease of interest were not involved in the design of the study.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 5.2, Benefit-Risk Assessment

Change: Section was added to clarify the potential benefits and risks of study participation.

Now reads:

Treatment with RTA 408 (omaveloxolone) provides the possibility of benefit based on the efficacy of omaveloxolone previously demonstrated in the present Study 408-C-1402, involving adult and adolescent participants with Friedreich's ataxia aged 16 years and older.

The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with omaveloxolone may be found in the Investigator's Brochure.

The potential risks related to participation in this study are justified by the anticipated benefit to participants. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study assessments and procedures.

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All safety findings will be closely monitored and reviewed by a data safety monitoring board (DSMB) in Part 1 and Part 2, and by the Sponsor during the extension phase of the study.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 7.6, Start of Study

Change: Section was added to include the definition of the start of the study.

Now reads:

The start of the study is the date the first participant signs the ICF.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 12.7, Reporting Serious Adverse Events

Change: Text was added to clarify the Sponsor's responsibilities in the study.

Now reads:

…

The Sponsor is to notify all appropriate regulatory authorities, EudraVigilance Database, IRBs, and investigators of SAEs, as required by local law, within required time frames.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 17.2, Ethical Conduct of the Study

Change: Text was added for adherence to EU regulatory requirements.

Now reads:

This clinical study was designed and shall be implemented and reported in accordance with the ICH E6(R1), with applicable local regulations (e.g., US CFR Title 21), **the requirements of Clinical Trials Regulation (EU) No 536/2014,** and with the ethical principles of the Declaration of Helsinki.

…

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Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 17.4, Confidentiality

Change: This section was updated to include a description of measures that will be implemented to ensure confidentiality of records and personal data of study participants.

Now reads:

…

The Sponsor will conduct this study, and process all personal data, according to the Sponsor policies related to data privacy, records retention and disposition, and information security. The Sponsor has developed, implemented, and will maintain a comprehensive, documented information security program that requires the implementation of administrative, physical, and technical safeguards to protect personal data against unauthorized or inappropriate use, access, or transmission. Such technical and organizational measures (including organizational processes and procedures) are designed to protect personal data from unauthorized use or access, accidental loss, damage, destruction, theft or disclosure, and to ensure that such measures are commensurate with the harm that may result from this. The Sponsor's information security controls are compliant with the National Institute of Standards and Technology Special Publication 800-53 (or the International Organization for Standardization equivalent) framework to protect the confidentiality of personal data.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

Section 18.1, Retention of Records

Change: This section was updated to include a description of measures that will be implemented in case of data security breach to mitigate potential adverse effects.

Now reads:

…

In case of a suspected data security breach, the Sponsor will follow the procedure outlined in its data privacy and information security policies, which require immediate reporting to the Sponsor's Global Privacy Office so that risk and next steps (including reporting to data protection authorities and/or data subjects) can be assessed.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

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Section 19, Publication Policy

Change: Text was added to clarify the policy for publication of the results of the study.

Now reads:

…

In accordance with international standards, the results of the clinical trial will be reported within one year from the end of the clinical trial and duly substantiated reasons will be provided by the Sponsor if the submission of the summary of the results of the clinical trial is after more than one year.

Sponsor publications will be developed, reviewed, and approved in accordance with current good publications practice guidelines and industry standards (e.g., International Committee of Medical Journal Editors recommendations; Good Publication Practice guidelines; The International Federation of Pharmaceutical Manufacturers and Associations Position; The Consolidated Standards of Reporting Trials guidelines; the Pharmaceutical Research and Manufactures of America Principles) to ensure that the publications reflect accurate, balanced, timely, and transparent reporting and interpretation of research data.

Rationale: This change was made in accordance with the EU CTR No 536/2014 guidance.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1.1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 5.1, Background and Rationale for RTA 408 in Friedreich's Ataxia

Change: Section was updated to add countries where omaveloxolone was approved for treatment of Fredreich's ataxia in adults and adolescents aged 16 years and older.

Now reads:

…

Additionally, omaveloxolone was approved for treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older in the following countries: Switzerland on 24 September 2024, United Arab Emirates on 30 October 2024, Kingdom of Bahrain on 25 November 2024, Chile on 06 January 2025, Kingdom of Saudi Arabia on 16 February 2025, Sultanate of Oman on 04 March 2025, State of Qatar on 12 March 2025, and Canada on 13 March 2025.

Rationale: Section was updated to reflect the most recent approval status of omaveloxolone.

Section 7.5, Data Safety Monitoring Board

Change: Section was updated to remove extension part of the study from the DSMB safety data review.

Now reads:

A DSMB will review unblinded safety data throughout the study (i.e., Part 1, Part 2)~~, and Extension~~ and make recommendations as appropriate. The DSMB will begin monthly data reviews approximately 1 month after the first patient is enrolled in Part 1 through the last dose of the last patient enrolled in Part 1. Part 2 ~~and Extension~~ data will be reviewed on a quarterly basis by the DSMB.

…

Rationale: This change was made to clarify that the review of safety data by the DSMB is only performed during Part 1 and Part 2 of the study.

Section 9.7.1, Women of Childbearing Potential

Change: Section was updated to remove bilateral tubal ligation and fallopian inserts with confirmed blockage from the definition of surgical sterility.

Now reads: Women of childbearing potential (WOCBP) are female patients who are not surgically sterile (no ~~history of bilateral tubal ligation,~~ hysterectomy or bilateral salpingo-oophorectomy), ~~do not have fallopian inserts with confirmed blockage,~~ have not had reproductive potential terminated by radiation or chemotherapy, and are not postmenopausal for at least 1 year.

Rationale: This change was made in accordance with the 2024 CTCG recommendations related to contraception and pregnancy testing in clinical trials.

Section 9.7.2, Methods of Birth Control

Change: Section was updated to add bilateral tubal occlusion as an acceptable method for birth control for women of childbearing potential and to clarify requirements for vasectomy.

Now reads:

…

- **Bilateral tubal occlusion**

…

- Have had a vasectomy (at least 6 months earlier) **with documented surgical success (e.g., absence of sperm in the ejaculate).**

Rationale: This change was made in accordance with the 2024 CTCG recommendations related to contraception and pregnancy testing in clinical trials.

Appendix 13, COVID-19 Mitigations; Section 4.1, United Kingdom Site

Change: References to the Investigator's Brochure version and specific sections in the Investigator's Brochure were removed.

Now reads:

…

Specifically, alternative mechanisms of oversight to liver function and BNP tests were employed based on benefit-risk assessment in the context of the guidance for Investigators provided in the Investigator's Brochure ~~version 6.1, sections 6.2.1 – Transaminases and GGT Elevations, 6.6.2 – Transient Elevation of Serum Transaminases, and 6.6.1 – Fluid Overload~~.

…

Rationale: This change was made to ensure consistency within the protocol.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The cover page was updated to replace the EudraCT Number with the EU CT Number.
- Typographical errors, grammar, and formatting were corrected.
- Section 4, List of Abbreviations, was updated.

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LIST OF ABBREVIATIONS

AE	adverse event
BNP	B-type natriuretic peptide
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CTCG	Clinical Trial Coordination Group
DSMB	data safety monitoring board
EU	European Union
EU CT	EU Clinical Trials
EU CTR	EU Clinical Trials Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
SAE	serious adverse event
US	United States
US IND	US Investigational New Drug
WOCBP	women of childbearing potential

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Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
5 Foundation Park
Roxborough Way
Maidenhead, Berkshire
SL6 3UD
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 408-C-1402

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia

Version 13

Date: 11 April, 2024

EU CT Number: 2015-002762-23

Version 13 of the protocol has been prepared for this amendment, which supersedes Version 12.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 408-C-1402 is to update the contraception language.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 9.7.2, Methods of Birth Control

Now reads:

~~From~~**Omaveloxolone is a weak CYP3A4 inducer. Concomitant use with omaveloxolone may reduce** the ~~Screening Visit, while taking study drug~~**efficacy of hormonal contraceptives; thus, they should not be the sole method of birth control.**

During screening, during the treatment period, and until ~~3 months after taking the~~ **28 days following administration of the** final dose of ~~study drug, WOCBP~~**omaveloxolone, females who are sexually active and of childbearing potential** must agree to practice ~~one~~**1** of the following **acceptable** methods of birth control:

- **Use of hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) as prescribed, plus a nonhormonal contraception method (cap, diaphragm, sponge with spermicide, or condom with or without spermicide).**
- **Use of an intrauterine hormone-releasing system as prescribed, plus a nonhormonal contraception method (cap, diaphragm, sponge with spermicide, or condom with or without spermicide).**
- **Use of a nonhormonal intrauterine device with appropriate reinsertion periodas prescribed.**
- **Vasectomized partner (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). Partner must be the sole partner for that participant.**
- **Abstinence from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.**

During screening, during the treatment period, and until 28 days after the final dose of omaveloxolone, fertile males who have female partners of childbearing potential must practice at least 1 of the following methods of birth control:

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- Have had a vasectomy (at least 6 months earlier).
- **Partner contraception methods; must be sole partner for that participant.**
- **Use of hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) as prescribed.**
- **Use of a nonhormonal intrauterine device with appropriate reinsertion period (as prescribed).**
- **Use of an intrauterine hormone-releasing system as prescribed.**
- Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm).
- ~~Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration~~
- ~~Use of an intrauterine device~~
- ~~Complete abstinence~~**Use of condoms with or without spermicide.**
- **Abstinence from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is** not **permitted**.
- ~~Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.) The vasectomized partner should be the sole partner for that subject.~~

~~From the Screening Visit, while taking study drug, and until 3 months after taking the final dose of study drug, males who have female partners of childbearing potential must agree to practice one of the following methods of birth control:~~

- ~~Have had a vasectomy (at least 6 months earlier)~~
- ~~Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm)~~
- ~~Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration~~
- ~~Partner use of an intrauterine device~~

~~Male patients must also agree to~~ **In addition, participants should not** donate sperm ~~starting on~~**or eggs for** the ~~first day~~**duration** of ~~treatment until approximately 3 months~~**the study and for at least 28 days** after **their** last dose of study ~~drug~~**treatment**.

Rationale: Omaveloxolone was approved by the Food and Drug Administration and by the European Medicines Agency; therefore, the contraception language was updated to align with the approved product label.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

No other major changes were made.

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SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Sponsor information was updated.
- Signature page was updated per Biogen SOP and responsible signatory.
- Table 1 was deleted because it was not required per Biogen template.
- Section 5.1, Background and Rationale for RTA 408 in Friedreich's Ataxia, was updated to include approval information for the United States and Europe.
- Section 7.6.1, End of Study, was added to include language ensuring that the study drug will be provided after the end of study until it is available through commercial channels or alternate post-trial access mechanisms. This language was also added to the Synopsis and to Section 7.1, Overall Study Design, for consistency.
- Section 12.7, Reporting Serious Adverse Events, was updated to remove references to [redacted].

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LIST OF ABBREVIATIONS

None.

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AMENDMENT CHANGE DOCUMENT

CLINICAL STUDY PROTOCOL 408-C-1402

A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015
Version 05	29 September 2015
Version 06	23 May 2016
Version 07	13 April 2017
Version 08	29 June 2017
Version 09	17 August 2017
Version 10	08 May 2020
Version 11	21 June 2021
Version 12	14 November 2022

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 11.0 to produce the text of Version 12.0. Additionally, the following points are provided.

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strike through~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in thesynopsis have not been described.
- Section numbers refer to the numbers in the new version of the protocol.
- Grammatical corrections and minor editorial changes are not described.

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Section	Protocol Version 12.0	Rationale
Sponsor Approval Signature Page	Updated Sponsor Signatories	Update due to personnel change
Table 1: Emergency Contact Information	[redacted] **change:** **From:** [redacted]~~, M.D.~~ [redacted] ~~Reata Pharmaceuticals, Inc~~ ~~Office:~~ [redacted] **To:** [redacted], M.D., Ph.D. [redacted] Reata Pharmaceuticals, Inc Office: [redacted] [redacted] **change:** **From:** [redacted] [redacted]- [redacted] ~~Reata Pharmaceuticals, Inc.~~ ~~Office:~~ [redacted] **To:** [redacted] [redacted] [redacted] Reata Pharmaceuticals, Inc. Office: [redacted]	To inform of update in study team from last protocol version.

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Section	Protocol Version 12.0	Rationale
Section 7.5 Data Safety Monitoring Board	Safety data of the open-label extension study is overseen by Reata's internal safety management team.	Changed to clarify how safety data is assessed during the open-label extension
Section 7.7 Schedule of Assessments Table 5: Extension Schedule of Assessments	*Added footnote [k] to Week 24 + and End of Study (EoS) visits:* [k] At week 24+ visits and end of study visit patients should be asked whether they had a recent electrocardiogram and/or echocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.	Added long-term exposure monitor of cardiac safety by
Section 9.1 Description of Study Drug (Extension)	Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules or 1 bottle containing 90 count of active (RTA 408 50 mg) capsules.	Updated to reflect all possible kit formats used on this study
Section 9.2 Prior and Concomitant Medications	9.2.2. Prohibited Medications	Added section header to divide between excluded and prohibited Medications for clarity.

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Section	Protocol Version 12.0	Rationale
Section 9.2.2. Prohibited Medications	The following medications and medication classes are not permitted during the extension study: • ~~Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil)~~ • Systemic moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice, cannabidiol, fluvoxamine, verapamil, diltiazem) • ~~Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)~~ If a patient takes a prohibited medication during the study, the investigator should notify the Medical Monitor immediately.	This change is included to align the protocol with IB version 8 - based on DDI study going forward only systemic moderate or strong inhibitors or inducers of Cytochrome P450 3A4 are prohibited, and to remind the sites to keep sponsor informed of any potential deviations regarding prohibited medications.
Section 9.2.3 Permitted Medications	~~9.2.2~~9.2.3 **Permitted Medications**	Updated section header numbering for Permitted Medications due to the addition of section 9.2.2 Prohibited Medications
Section 9.9.9. Echocardiogram	During the extension, at week 24+ visits and end of study visit, patients should be asked whether they had a recent echocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.	Added to monitor long-term exposure of cardiac safety
Section 9.9.10. Electrocardiogram	During the extension, at week 24+ visits and end of study visit, patients should be asked whether they had a recent electrocardiogram done. If the answer is yes, the site is to request that data and, if provided, enter that data in the appropriate eCRF.	Added to monitor long-term exposure of cardiac safety

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Section	Protocol Version 12.0	Rationale
Section 9.9.24. Study Drug Administration (Extension)	Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules or 1 bottle containing 90 count of active (RTA 408 50 mg) capsules.	Updated to reflect all possible kit formats used for the study
Section 9.9.29. 25-Foot Timed Walk Test	If a patient uses an assistive device for the 25-foot timed walk test on Day 1, the same assistive device should ~~must~~ be used for all 25-foot walk assessments, when possible.	This update is to consider when patients with disease progression may need to change their assistive devices
Section 10.2. Study Drug Packaging and Labeling	Treatment kits containing ~~three, four, or~~ up to six bottles, depending on treatment assignment, will be provided to patients for self-administration. Each bottle will contain 30 or 90 capsules and a desiccant insert that must not be ingested.	Updated to reflect all possible kit formats used for the study
Appendix 13. COVID-19 Mitigations: Section 1. Site Operations & Patient Management	Updates are to be sent to the Sponsor study team [redacted].	Email address will no longer be used for this study

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Section	Protocol Version 12.0	Rationale
Appendix 13. COVID-19 Mitigations: Section 2. COVID-19 Testing and Investigational Product Use	If a patient enrolled in the Extension phase of Study 408-C-1402 tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the investigational product (IP) RTA-408 (omaveloxolone) must be temporarily discontinued until the patient no longer presents an active infection, defined as resolution of symptoms or a negative test, as assessed by the Investigator and/or the patient's physician(s). The Sponsor must be notified immediately for additional guidance. **2.1. Resumption of Investigational Product after Recovery from COVID-19 Infection** The duration of treatment interruption due to COVID-19 infection must be determined based on the patient's symptoms and the investigator's discretion. Patients who interrupt treatment for no more than 14 days may resume study drug without an in-person visit, at the investigator's discretion, if COVID-19 symptoms have resolved or a negative test is presented. ~~When~~ If the duration of treatment interruption exceeds 14 days and the investigator deems that the patient can safely ~~return to the site for~~ complete an in-person visit, the investigator should conduct an unscheduled visit and perform all assessments as in Week 4. If there are no changes in clinical status that would preclude resuming IP, IP may be resumed. A follow-up telephone visit should be conducted approximately 2 weeks after this unscheduled visit to collect adverse events and prior and concomitant medications. Approximately ~~F~~four weeks after the unscheduled visit, the patient should return for repeat assessments as in the Week 4 visit. The usual visit schedule may resume thereafter. If an in-clinic visit is not possible, visits can be conducted as a combination of a telephone visit and a home health nurse visit.	Updated to include more definitive guidelines for managing COVID-19 infections while on study

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Section	Protocol Version 12.0	Rationale
Appendix 13. COVID-19 Mitigations: Section 3. Investigational Product (IP) Access	~~Stability information for IP shipments are contained in the "Guidance for Direct-to-Patient Shipping of RTA 408 Drug Product Capsules during the Coronavirus (COVID-19) Pandemic" (Attachment 1).~~ All shipments must be sent via overnight express shipping (where possible). ~~and~~ Shipments should include a temperature monitoring device if required based on sponsor guidance. *Removed Attachment 1*	Updated to remove reference to COVID-19 mitigations guidance and include global shipping requirements within the protocol based on additional stability information

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AMENDMENT CHANGE DOCUMENT

CLINICAL STUDY PROTOCOL 408-C-1402

A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015
Version 05	29 September 2015
Version 06	23 May 2016
Version 07	13 April 2017
Version 08	29 June 2017
Version 09	17 August 2017
Version 10	08 May 2020
Version 11	21 June 2021

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 10.0 to produce the text of Version 11.0. Additionally, the following points are provided.

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strike through~~.
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Section	Protocol Version 11.0	Rationale
Sponsor Approval Signature Page	Updated Sponsor Signatories	Update due to personnel change
Table 1: Emergency Contact Information	[redacted] **Change:** **From:** [redacted]~~, M.D.~~ [redacted] ~~Reata Pharmaceuticals, Inc~~ ~~Office:~~ [redacted] **To:** [redacted], M.D. [redacted] Reata Pharmaceuticals, Inc Office: [redacted] **Reata Pharmaceuticals Address change:** **From:** ~~2801 Gateway Drive, Suite 150~~ ~~Irving, TX 75063~~ **To:** 5320 Legacy Drive Plano, Texas 75024 **Reata Pharmaceuticals** [redacted] **Email Contact Change:** **From:** Email: [redacted] **To:** Email: [redacted]	To inform of update in study team and safety monitoring provider from last protocol version.

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Section	Protocol Version 11.0	Rationale
Table 5: Extension Schedule of Assessments	Added Clinical Chemistry, Hematology, Urinalysis and microscopy, and BNP and NT pro-BNP to Assessments at Week 24+ Every 24 Weeks Visits	Changed to include required Safety laboratory assessments in extension Week 24 and beyond for long term safety surveillance and data collection
Table 5: Extension Schedule of Assessments	Added Clinical Chemistry, Hematology, Urinalysis and microscopy, BNP and NT pro-BNP, and Pregnancy test WOCBP to Assessments at End of Study Visit	Changed to include required Safety laboratory assessments and pregnancy tests at End of Study
Section 9.1.1 Management of Elevated Transaminase Levels (ALT and/or AST)	Transaminases should be monitored using data from the scheduled lab draws in Part 2 and the extension. ~~and should continue to be monitored in the extension following the patient's standard of care.~~	Changed to reflect mandatory lab draws to monitor AST/ ALT during extension for long term safety surveillance and data collection
Section 9.9 Study procedures	~~Home health assessments are not permitted during the extension.~~ During the extension every effort should be made to ensure patient assessments are performed on-site. If this is not possible home health visits are acceptable. For more detail regarding use of home health services see Appendix 13 (COVID-19 Mitigations).	Changed to reflect mitigations due to the COVID-19 pandemic
Section 9.9.15 Clinical Chemistry	Added: Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator.	Added the possibility to use local labs for monitoring of patient safety if central labs cannot be collected
Section 9.9.16 Hematology Assessments	Added: Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator.	Added the possibility to use local labs for monitoring of patient safety if central labs cannot be collected
Section 9.9.17 Urinalysis and Microscopy	Added: Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator.	Added the possibility to use local labs for monitoring of patient safety if central labs cannot be collected

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Section	Protocol Version 11.0	Rationale
Section 9.9.18 N-Terminal Prohormone of B-Type Natriuretic Peptide and B-Type Natriuretic Peptide	Added: Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator.	Added the possibility to use local labs for monitoring of patient safety if central labs cannot be collected
Section 9.9.37 Home Health Visits	9.9.37. Home Health Visits ~~(Part 1 and Part 2)~~ For Part 1 and Part 2 patients at approved sites will have the option of having a home health visit at the Screening Visit (all patients, Part 1 and Part 2) and Visit 3 (Part 1 only). During the extension every effort should be made to ensure patient assessments are performed on-site. If this is not possible home health visits are acceptable. For more detail regarding use of home health services see Appendix 13 (COVID-19 Mitigations).	Changed to reflect mitigations due to the COVID-19 pandemic
Section 12.1 Safety Parameters	Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-proBNP, and pregnancy tests [as indicated])	Changed to include required Safety laboratory assessments in all visits during the extension for long term safety surveillance and data collection
Table 10: Serious Adverse Event Reporting Contact Information	Medical Monitor Team Reata Pharmaceuticals, Inc. Office: [redacted] Email: [redacted]	To inform of update in medical monitor team email address from last protocol version.
Section 14.2.4 Safety Variables	Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-proBNP, and pregnancy tests [as indicated])	Changed to include required Safety laboratory assessments in all visits during the extension for long term safety surveillance and data collection

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Section	Protocol Version 11.0	Rationale
Appendix 13 COVID-19 Mitigations Section 3 – Investigational Product (IP) Access	~~For shipments anticipated to exceed the 48 hour interval.~~All shipments must be sent via overnight express shipping (where possible) and include a temperature monitoring device. Sites will be supplied with temperature monitors upon request. For shipments that ~~exceed 48 hours of transit time~~ show temperature excursions below 20C or above 25C during transit, the Sponsor should be notified immediately via the COVID-19 Investigational Product Temperature Excursion form.	Updated to reflect updated acceptable shipment guidelines

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Section	Protocol Version 11.0	Rationale
Appendix 13 COVID-19 Mitigations	4. STUDY VISIT Where in-person clinic visits are not possible, in-home visits and/or telemedicine visits (e.g. phone or video) may be conducted to complete study assessments not limited to: ~~Where inadvisable for the patient to be seen for an in-person clinic visit, visits may be conducted via telemedicine (e.g., phone or video). At a minimum, telemedicine visits for all sites should complete the following assessments:~~ • Adverse event assessment. • Prior and concomitant medication assessment. Pregnancy testing for women of childbearing potential (WOCBP): patients must complete scheduled urine pregnancy tests at home. Pregnancy test(s) should be provided to patients where relevant. The site should obtain verbal confirmation from the patients that the test is negative prior to instructing the patients to start the shipped RTA-408 IP. Additionally, the site will specifically remind patients of the need to adhere to appropriate protocol required contraceptive measures where necessary. ~~4.1. Sites in Australia, Austria, Italy, and United States~~ ~~Where in-person clinic visits are not possible, in-home visits may be provided in these specific geographies by home health services to perform the following non-exclusive assessments:~~ ~~• Urine pregnancy tests for WOCBP (where applicable).~~ • Vital signs. • Safety labs: ~~(not required, may be performed upon site request).~~ Every effort should be made to collect laboratory data using the central lab. Where use of the central lab is not possible, laboratory assessments should be collected through a local lab and reviewed by the investigator. ~~4.2.~~4.1. United Kingdom Site	Changed to include required Safety laboratory assessments in all visits during the extension for long term safety surveillance and data collection

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AMENDMENT CHANGE DOCUMENT

CLINICAL STUDY PROTOCOL 408-C-1402

A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015
Version 05	29 September 2015
Version 06	23 May 2016
Version 07	13 April 2017
Version 08	29 June 2017
Version 09	17 August 2017
Version 10	08 May 2020

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 9.0 to produce the text of Version 10.0. Additionally, the following points are provided.

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- Grammatical corrections and minor editorial changes are not described.

Section	Protocol Version 10.1	Rationale
Table 1 Emergency Contact Information AND Section 12.7 Reporting Serious Adverse Events	**From:** [redacted] ~~MS,~~ [redacted] ~~Reata Pharmaceuticals, Inc.~~ ~~2801 Gateway Drive, Suite 150~~ ~~Irving, TX 75063~~ ~~Office:~~ [redacted] ~~Mobile:~~ [redacted] ~~Email:~~ [redacted] **To:** [redacted] M.D. [redacted] Reata Pharmaceuticals, Inc. 2801 Gateway Drive, Suite 150 Irving, TX 75063 Office: [redacted] **Added:** [redacted] Reata Pharmaceuticals, Inc. 2801 Gateway Drive, Suite 150 Irving, TX 75063 Office: [redacted]	To inform of update in study team and safety monitoring provider from last protocol version.

Section	Protocol Version 10.1	Rationale
	From: [redacted] ~~MD~~ ~~Reata Pharmaceuticals, Inc.~~ ~~2801 Gateway Drive, Suite 150~~ ~~Irving, TX 75063~~ ~~Mobile:~~ [redacted] ~~Email:~~ [redacted] **To:** Medical Monitor Team Reata Pharmaceuticals, Inc. 2801 Gateway Drive, Suite 150 Irving, TX 75063 Office: [redacted] Email: MedMon@Reatapharma.com **From:** ~~Serious Adverse Event (SAE) Reporting~~ [redacted] ~~Telephone:~~ [redacted] ~~Facsimile:~~ [redacted] ~~Email:~~ [redacted] ~~SAE Hotline:~~ [redacted] ~~Safety Fax:~~ [redacted] **To:** [redacted] Email: [redacted] Fax: [redacted]	

Section	Protocol Version 10.1	Rationale
Section 5.1 Background and Rationale for RTA 408 in Friedreich's Ataxia AND Section 20 List of References	~~These results indicated that activation of PGC-1α, an Nrf2 target gene, led to increased mitochondrial biogenesis (Wenz, 2008).~~ ~~Wenz T, Diaz F, Spiegelman BM, *et al*. Activation of the PPAR/PGC-1α pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype. Cell Metab 2008;8:249-256.~~	Sentences/reference removed because the cited article has been retracted.
Section 7.1 Overall Study Design	The conduct of the extension phase, according to protocol specifications, was impacted by the COVID-19 (Coronavirus Disease 2019) pandemic. As a result, and as of Version 10 of the protocol, modifications intended to address access to and administration of investigational product, and adherence to protocol-specified visits and laboratory assessments was implemented. These modifications are described in Appendix 13 (COVID-19 Mitigations).	To indicate, in the body of the Study Protocol, the inclusion of a COVID-19 Mitigations appendix. Refer to the Appendix 13 entry below for additional information.
Section 7.7 Schedule of Assessments Table 5: Extension Schedule of Assessments	"Height" row added. Footnote added: [j] Height will be performed at Week 4 for Part 2 patients enrolled in the Extension.	To provide clarification in regards to height measurements for Part 2 participants enrolled in the Extension phase. These clarifications are in agreement with the Protocol Clarification Memorandum issued on February 18, 2019.
Section 8.3 Extension Eligibility AND Appendix 1 Extension Eligibility Criteria	7. Have been enrolled in Part 1 or Part 2 and completed assessments through the follow-up visit with no major protocol deviations that would, in the opinion of the investigator, deem the patient unsuitable for enrollment in the Extension phase of the study.	To provide clarification on the meaning of "major protocol deviations" for enrollment criteria in the Extension phase of Study 408-C-1402. The clarification is in agreement with the Protocol Clarification Memorandum issued on October 08, 2018.

Section	Protocol Version 10.1	Rationale
Section 8.4 Patient Rescreening	Patients may repeat the screening procedures ~~once~~ to qualify for the study if they have: Patients may repeat the screening procedures once to qualify for Parts 1 and 2 of the study. For the extension, patients may be rescreened at the discretion of the Sponsor, following discussion with the investigator site.	To provide clarification in regards to patient rescreening for each phase of Study 408-C-1402. These clarifications are in agreement with the Protocol Clarification Memorandum issued on June 10, 2019.
Appendix 2 Maximal Exercise Test AND Appendix 3 FARS ASSESSMENT	Appendices added.	Documents outlining the procedures for the maximal exercise testing and FARS assessment were included for completeness.
Appendix 13 COVID-19 Mitigations	Appendix added.	The Appendix 13 "COVID-19 Mitigations" was created in response to challenges in the conduct of Study 408-C-1402 trial during the COVID-19 pandemic. The appendix outlines mitigation strategies to address issues related to access and administration of investigational product and adhesion to protocol-specified visits and laboratory assessments. A population benefit/risk analysis ensuring the health and safety of trial participants, whilst maintaining compliance with good clinical practice and minimizing the risk to trial integrity, was used as the basis for developing the mitigation approach outlined in this appendix.



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Protocol History

Version 01	23 July 2014
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Version 09	17 August 2017

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 8 to produce the text of Version 9. Additionally, the following points are provided.

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Section	Protocol Version 9	Rationale
Section 6.2.1 Primary Objective	• To evaluate the change in the modified Friedreich's ataxia rating scale (mFARS) score at Week 48 ~~24~~	Part 2 study duration extended to 48 weeks
Section 6.2.2 Secondary Objectives	• To evaluate the change in peak work during maximal exercise testing at Week 48~~24~~ • To evaluate the Patient Global Impression of Change at Week 48~~24~~ • To evaluate the Clinical Global Impression of Change at Week 48~~24~~	Part 2 study duration extended to 48 weeks
Section 6.2.3 Exploratory Objectives	• To evaluate the distribution of change in mFARS scores at Week 48~~24~~	Part 2 study duration extended to 48 weeks
Section 7.1 Overall Study Design	Following randomization on Day 1, patients will self-administer study treatment once daily for 48~~24~~ weeks. A follow-up visit for safety will occur at Week 52 ~~28~~ (4 weeks after last dose).	Part 2 study duration extended to 48 weeks
Section 7.1 Overall Study Design	Since Part 2 patients will be followed continuously within the study, eligibility for the extension should be assessed at the Week 52 ~~28~~ visit and a separate screening visit is not required. After confirming eligibility for Part 2 patients, study treatment for extension Day 1 should be dispensed following the Week 52 ~~28~~ assessments.	Part 2 study duration extended to 48 weeks
Section 7.4.1 Overall Study Design	Based on these considerations, an RTA 408 dose of 150 mg was selected for Part 2 because it differs by less than 10% from the 160-mg dose that was evaluated in Part 1 and therefore is expected to provide similar systemic exposure while affording a reduction in the number and complexity of capsules that patients are required to swallow once each day for 48 ~~24~~ weeks during Part 2.	Part 2 study duration extended to 48 weeks
Section 7.4.2 Dose-Escalation Scheme	Part 2: Dose-escalation or de-escalation will not be used in Part 2. Patients randomized to RTA 408 will receive 150 mg of RTA 408 daily throughout the 48 ~~24~~ -week treatment period.	Clarification and Part 2 study duration extended to 48 weeks
Table 4 Schedule of Assessments	Added visits at Weeks 30 (telephone), 36, 42 (telephone), 48, and 52	Changed to reflect updated study design
Table 4 Schedule of Assessments	[k] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Day 14 (Visit 4), Day 84 (Visit 7), Day 168 (Visit 9), and Day 336 (Visit 13) after the blood collection for predose PK analysis. All other doses can be administered at home. Study drug should be administered once daily through Day ~~168~~ 336 (Visit ~~9~~ 13).	Updated study drug administration based on study design

Section	Protocol Version 9	Rationale
Table 4 Schedule of Assessments	[s] Patients will be provided the fall diary at Screening and must record fall incidents between Screening and Week 48 ~~24~~.	Part 2 study duration extended to 48 weeks
Table 4 Schedule of Assessments	[u] A single blood sample for PK analysis at Day 84 (Visit 7) , Day 168 (Visit 9), and Day 336 (Visit 13) should be collected prior to study drug administration.	Part 2 study duration extended to 48 weeks
Table 5 Schedule of Assessments	[a] The screening visit is only required for Part 1 patients. Assessments collected at Part 2 - Week 48 ~~24~~ or Part 2 - Week 52 ~~28~~ should be used to assess eligibility for Part 2 patients.	Updated to reflect longer Part 2 duration
Table 5 Schedule of Assessments	[d] For patients enrolled in Part 2 of the study, visit procedures required at Week 52~~28~~ and also Extension Day 1 should only be performed once since Part 2 Week 52~~28~~ and Extension Day 1 should occur on the same day.	Updated to reflect longer Part 2 duration
Section 8.3 Extension Eligibility	Patients must complete 12 weeks of treatment in Part 1, or 48~~24~~ weeks of treatment in Part 2, have no major protocol deviations, and continue to meet inclusion and exclusion criteria as specified in Appendix 1.	Part 2 study duration extended to 48 weeks
Section 9.3 Compliance with Study Drug	To be considered compliant with study drug, patients can miss no more than 25% of the total planned doses (i.e., 21 doses during Part 1, or 84 ~~42~~ doses during Part 2) during the study.	Part 2 study duration extended to 48 weeks
Section 9.9 Study Procedures	All assessments occur in the study center clinic with the exception of those assessments for lab collection at Screening (all patients, Part 1 and Part 2) and Visit 3 (Part 1 only), which may be performed by a home health visit nurse (at appropriate locations and approved by Sponsor) and those assessments for Visits 6 and 8 in Part 1 and Visits 3, 6, 10 and ~~6~~ 12 in Part 2, , which will be performed via telephone contact.	Part 2 study duration extended to 48 weeks
Section 9.9.5 Foot X-Ray	Patients should complete the foot x-ray at Screening; however, if a patient was not able to complete the foot x-ray at Screening, it may be completed at any point during the first 52 ~~28~~ weeks of the study.	Part 2 study duration extended to 48 weeks

Section	Protocol Version 9	Rationale
Section 9.9.24 Study Drug Administration	Study drug should be taken with water at the times indicated in Table 4, except on Days 1, 14, 84, and 168 and 336, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, 84, 168, and 336. The date and time of the 2 most recent doses of study medication prior to Days 14, 84, and 168, will be recorded for PK analysis. The date and time of the last study drug administration (Day 336 ~~168~~) should be recorded.	Part 2 study duration extended to 48 weeks
Section 9.9.35 Falls Diary	Patients will be provided the fall diary at Screening and must record fall incidents between Screening and Week 48 ~~24~~.	Part 2 study duration extended to 48 weeks
Section 11.2.1 Friedreich's Ataxia Rating Scale	The change in both the FARS neurological score and the modified FARS scores from Baseline to Weeks 4, 12, 18, 24, 36, and ~~24~~48 will be analyzed.	Part 2 study duration extended to 48 weeks
Section 11.2.2 Patient Global Impression of Change	The proportion of patients who are a treatment success at Weeks 12, 24, 36, and ~~24~~48, based on the Patient Global Impression of Change.	Part 2 study duration extended to 48 weeks
Section 11.2.3 Clinical Global Impression of Change	The proportion of patients who are a treatment success at Weeks 12, 24, 36, and ~~24~~48, based on the Clinical Global Impression of Change.	Part 2 study duration extended to 48 weeks
Section 11.2.4 Maximal Exercise Test	The changes in peak work and oxygen utilization during maximal exercise testing from Baseline to Weeks 4, 12, 18, 24, 36, and ~~24~~48will be analyzed.	Part 2 study duration extended to 48 weeks
Section 11.2.5 9-Hole Peg Test	The change in performance on the 9-HPT from Baseline ~~to Week~~ at Weeks 24 and 48 will be analyzed.	Part 2 study duration extended to 48 weeks
Section 11.2.6 25-Foot Timed Walk Test	The change in performance on the 25-foot timed walk test from Baseline ~~to Week~~ at Weeks 24 and 48will be analyzed	Part 2 study duration extended to 48 weeks
Section 11.2.7 SF-36 Health Survey Update	The change in SF-36 patient-reported outcome scores from Baseline ~~to Week~~ at Weeks 24 and 48 will be analyzed.	Part 2 study duration extended to 48 weeks

Section	Protocol Version 9	Rationale
Section 11.2.8 Activities of Daily Living	The change in activities of daily living from Baseline at ~~to Week~~ at Weeks 24, 36, and 48 will be analyzed.	Part 2 study duration extended to 48 weeks
Section 11.2.9 Frequency of Falls	The frequency of falls from Screening through Week 48 ~~24~~ will be analyzed.	Part 2 study duration extended to 48 weeks
Section 11.2.10 Distribution of Change in mFARS Scores	The proportion of patients at Week 48 ~~24~~ with an mFARS change from baseline at or lower than specified cutoff values defined in the SAP (e.g., -2, -3, etc) will be analyzed.	Part 2 study duration extended to 48 weeks
Section 14.1 Sample Size	[redacted]	Part 2 study duration extended to 48 weeks
Section 14.3.2 Primary Efficacy Analysis	All scheduled efficacy values collected through the end of treatment visit (i.e., Week 12 in Part 1, Week ~~24~~ 48 in Part 2) will contribute to the primary analysis.	Part 2 study duration extended to 48 weeks
Section 17.2 Ethical Conduct of the Study	Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ ~~http://www.wma.net/en/30publications/10policies/b3/].~~	Updated URL
Appendix 5	Added Patient Global Impression of Change	Clarification
Appendix 6	Added Clinical Global Impression of Change	Clarification



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Section	Protocol Version 8	Rationale
Section 6.2.2 Secondary Objective	• To evaluate the Patient Global Impression of Change at Week 24 • To evaluate the Clinical Global Impression of Change at Week 24	Added Patient Global Impression of Change and Clinical Global Impression of Change as secondary endpoints
Section 6.2.3 Exploratory Objectives	• To evaluate the distribution of change in mFARS scores at Week 24	Added the distribution of change of mFARS scores at Week 24 as an exploratory endpoint
Table 4 Schedule of Assessments	Foot X-ray, video collection of normal walking, patient global impression of change, and clinical global impression of change added to Part 2 assessments.	Additional assessments have been added to obtain additional baseline information and additional information regarding potential drug effects
Table 4 Schedule of Assessments	[d] Only 1 x-ray will be collected during the study. Only x-rays of the right foot will be completed for the foot x-ray assessment. Patients should complete the x-ray foot assessment at Screening; however, if the patient was not able to complete the x-ray foot assessment at Screening, it may be completed during any visit while the patient is participating in the study.	Details surround foot x-ray assessment added
Table 4 Schedule of Assessments	[p] Video of the 25-foot timed walk test is optional and will be collected only for those patients who provide consent to video. [q] Patients who consent to video collection of the 25-foot timed walk test will also have video collection during normal walking with a 25-foot (un-timed) walk using his/her normal gait. The normal walk must be performed after the 25-foot timed walk test.	Details surround video collection of normal walking and during the 25-foot timed walk test added
Table 4 Schedule of Assessments	[r] Patients and investigators must complete the patient global impression of change and clinical global impression of change following completion of the neurological FARS exam.	Provide clarification regarding timing of assessments
Table 5 Schedule of Assessments	[i] Patients and investigators must complete the patient global impression of change and clinical global impression of change following completion of the neurological FARS exam.	Provide clarification regarding timing of assessments

Section	Protocol Version 8	Rationale
Section 9.9.1 Informed Consent	Patients have the option to separately consent to have video recorded during the 25-foot timed walk and 25-foot normal walk tests at selected sites.	Included clarification about additional consent for video recording
Section 9.9.5 Foot X-Ray	The foot x-ray assessment will be performed to quantify the foot structure of patients with and without pes cavus. Specific radiological angles of the foot will be quantified by a central reader. Radiological angles assessed from a lateral image of the foot may include but are not limited to: tibia-talar angle, talo-calcaneal angle, tibia-calcaneal angle, talo-first metatarsal angle, calcaneal pitch angle, and naviculocuboid overlap. The x-ray of the lateral view of the right foot will be collected once per patient at the time indicated in Table 4. Patients should complete the foot x-ray at Screening; however, if a patient was not able to complete the foot x-ray at Screening, it may be completed at any point during the first 28 weeks of the study.	Added details regarding foot X-ray assessment
Section 9.9.29 25-Foot Timed Walk Test	Patients will have the option to consent to video recording during the 25-foot timed walk test at selected sites. Video recording for the 25-foot timed walk test is optional. Procedures for video collection will be described in a separate study specific manual.	Added optional video recording of 25-foot timed walk test
Section 9.9.30 Video Collection of Patients Walking 25-ft with Their Natural Gait	Patients who consent to video collection of the 25-foot timed walk test will also have video collection during normal walking with a 25-foot (un-timed) walk using his/her normal gait, at the times indicated in Table 4. The normal walk must be performed after the 25-foot timed walk test. Procedures for video collection will be described in a separate study specific manual.	Added optional recording of patients walking with natural gait
Section 9.9.33 Patient Global Impression of Change	The Patient Global Impression of Change is a 7-point scale that requires the patient to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention (Guy 1976). Patients will be instructed to complete the Patient Global Impression of Change survey at the times indicated in Table 4. The patient global impression of change is assessed by completing the following statement "since I began trial treatment, my overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)." Patients must complete this assessment following completion of the FARS neurological assessment or the clinical global impression of change.	Added efficacy endpoint

Section	Protocol Version 8	Rationale
Section 9.9.34 Clinical Global Impression of Change	The Clinical Global Impression of Change is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention (Guy 1976). Clinicians will be instructed to complete the Clinician Global Impression of Change survey at the times indicated in Table 4. The clinician global impression of change is assessed by completing the following statement "Compared to the patient's condition at the start of the trial, this patient's overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)." Clinicians may take into account prior results of study assessments to influence their clinical judgement of the Clinician Global Impression of Change. Clinicians must complete this assessment following the patient's completion of the FARS neurological assessment or the patient global impression of change.	Added efficacy endpoint
Section 11.2.2 Patient Global Impression of Change	The proportion of patients who are a treatment success at Weeks 12 and 24, based on the Patient Global Impression of Change. A treatment success is defined as "Much Improved" or "Very Much Improved" on the Patient Global Impression of Change.	Provide detail regarding planned analysis
Section 11.2.3 Clinical Global Impression of Change	The proportion of patients who are a treatment success at Weeks 12 and 24, based on the Clinical Global Impression of Change. A treatment success is defined as "Much Improved" or "Very Much Improved" on the Clinical Global Impression of Change.	Provide detail regarding planned analysis
Section 11.2.10 Distribution of Change in mFARS Scores at Week 24	The proportion of patients at Week 24 with an mFARS change from baseline at or lower than specified cutoff values defined in the SAP (e.g., -2, -3, etc) will be analyzed.	Provide detail regarding planned analysis
Section 14.1 Sample Size	For multiple comparisons, the SAP will describe strict control of Type I error rate.	Clarification
Section 14.2.3 Efficacy Variables	Part 2: Efficacy variables are modified FARS scores, full FARS scores, peak work during maximal exercise testing, parameters collected during maximal exercise testing (other than peak work), 9-HPT scores, 25-foot timed walk test distance, ADL, Patient Global Impression of Change, Clinical Global Impression of Change, and SF 36 scores.	Added efficacy variables specific to Part 2
References	Guy, W. ECDEU Assessment Manual For Psychopharmacology, DHEW Publication No. ADM 76–338, US Government Printing Office, Washington, DC, USA, 1976.	Added reference cited in text



AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 408-C-1402
A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015
Version 05	29 September 2015
Version 06	23 May 2016
Version 07	13 April 2017

Confidentiality Statement

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 6 to produce the text of Version 7. Additionally, the following points are provided.

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strike through~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis have not been described.
- Section numbers refer to the numbers in the new version of the protocol.
- Grammatical corrections and minor editorial changes are not described.

Section	Protocol Version 7	Rationale
Cover Page	US IND NUMBER: 122,349 EUDRACT NUMBER 2015-002762-23	Added IND and EUDRACT numbers
Table 1	[redacted] MD ~~Trial Runners, LLC~~ Reata Pharmaceuticals, Inc ~~128 W. Villared~~ 2801 Gateway Drive, Suite 150 ~~Dickinson, ND 58601 USA~~ Irving, TX 75063 Office: [redacted] Mobile: [redacted] Email: [redacted]	Change in medical monitor
Global	Up to ~~12~~ approximately 20 study centers	Additional study sites included
Global	Estimated date first patient enrolled in Part 1: November 2014	Clarification
Global	Estimated date last patient completed Part 2: ~~December 2016~~ December 2018 Extended access until commercial availability of RTA 408	Clarification
Section 6.2 Part 2 Objectives	Added section	Added Part 2 objectives to separate study objectives between Part 1 and Part 2
Section 6.2.3 Exploratory Objectives	• To evaluate the change in the Activities of Daily Living (ADL) score • To evaluate the frequency of falls	Added activities of daily living and the frequency of falls as exploratory endpoints
Section 6.3 Extension	The objective of the extension is to provide continuing treatment with RTA 408 as part of this extended access program while collecting ongoing safety and tolerability data with RTA 408.	Added objectives for the extension study
Section 7.1 Overall Study Design	This ~~2 part~~ study will evaluate the efficacy, safety, and PD of RTA 408 in the treatment of patients with Friedreich's ataxia. A schema summarizing the study parts and cohorts is shown in Figure 1 and Figure 2.	Clarification

Section	Protocol Version 7	Rationale
Section 7.1 Overall Study Design	Up to approximately 9 cohorts will be enrolled in Part 1 of the study to allow for adequate dose-ranging for selection of ~~two doses~~ a dose of RTA 408 to be used in Part 2.	Clarification based on Part 2 study design
Section 7.1 Overall Study Design	Part 2: The second part of this study will be a randomized, placebo-controlled, double-blind, parallel ~~study~~ group study to evaluate the safety, and efficacy of ~~2 dose levels~~ of RTA 408 150 mg in patients with Friedreich's ataxia~~. Assuming that doses tested in Part 1 have been deemed acceptable in the first part of the study, the first 24 eligible patients in Part 2~~ Patients enrolled in Part 2 will be randomized 1:1~~:1~~ to receive RTA 408 ~~at the~~150 mg, or placebo. Randomization will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will comprise no more than 20% of patients enrolled in Part 2. The RTA 408 dose of 150 mg was selected ~~doses, or placebo (n=8 per treatment group). The two doses to be selected are~~ for Part 2 based on DSMB and Sponsor review of available data from Part 1, including ~~available~~ safety, efficacy, PK and PD data.	Changed to a single dose versus placebo in Part 2 and randomization stratified by pes cavus status.
Section 7.1 Overall Study Design	Following randomization on Day 1, patients will ~~be stratified by peak work at baseline (>0.8 watts [W]/kg vs. ≤0.8 W/kg).~~self-administer study treatment once daily for 24 weeks. A ~~blinded sample size recalculation~~ follow-up visit for safety will occur at Week 28 (4 weeks after ~~the~~ last ~~patient is enrolled in Part 2 to evaluate the distribution of baseline peak work for all enrolled patients as described in Section 14.1.1 and assess the need for additional patients. If the sample size recalculation demonstrates additional patients are needed, then expansion of the number of patients enrolled in Part 2 will occur and an additional 12 patients may be randomized, for a total of 36 patients enrolled in Part 2 (n=12 per treatment group).~~ dose). The DSMB will perform quarterly reviews of unblinded data for safety throughout Part 2.	Removed sample size recalculation
Section 7.1 Overall Study Design	~~A schema for the protocol is shown in Figure 1 and a detailed schedule of assessments for the study is shown in Table 3. All qualified patients enrolled in the study (i.e., both Part 1 and Part 2) will follow nearly identical schedules of assessments (Table 3) and study drug administration. Patients will self-administer study treatment once daily until they have completed 12 weeks (84 days) of study treatment, are discontinued from study treatment, or have withdrawn consent to participate in the study. A follow-up visit for safety will occur at Week 16 (4 weeks after last dose). The DSMB will perform monthly reviews of unblinded data for safety throughout the study (i.e., during both Part 1 and Part 2).~~	Removed dosing instructions from study design section

Section	Protocol Version 7	Rationale
Section 7.1 Overall Study Design	Extension: The extension will assess long-term safety and tolerability of RTA 408 in qualified patients with Friedreich's ataxia following completion of Part 1 or Part 2. Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study. Patients will receive open-label RTA 408 (150 mg) once daily until the drug is available through commercial channels, or until patient withdrawal, whichever is sooner. All patients in the extension will follow the same visit and assessment schedule. Extension Day 1 is defined as the first day treatment is dispensed to the patient for the extension, following completion of Part 1 or Part 2. All other extension visits will be relative to extension Day 1. Patients will be scheduled for in-person assessments during treatment in the extension at Day 1, Week 4, Week 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Day 14. Since Part 2 patients will be followed continuously within the study, eligibility for the extension should be assessed at the Week 28 visit and a separate screening visit is not required. After confirming eligibility for Part 2 patients, study treatment for extension Day 1 should be dispensed following the Week 28 assessments. Part 1 patients will not have been followed continuously within this study, and therefore must complete a screening visit to confirm eligibility.	Added study design description for the extension study
Section 7.2 Number of Patients	Up to approximately ~~108~~ 172 patients will be enrolled in this study (up to 72 patients in Part 1 and approximately 100 patients in Part 2). The extension will only include qualified patients from Part 1 and Part 2, as outlined in Section 8.3.	Number of patients updated to reflect changes in Part 2 study design
Section 7.3 Treatment Assignment	Part 2: One dose ~~levels~~ level of RTA 408 within the dose-range evaluated in Part 1 will be used in Part 2. Patients enrolled in Part 2 of the study will be randomized 1:1~~:1~~ to RTA 408 ~~low dose, RTA 408 high dose,~~150 mg or placebo. Part 2 randomization will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will not comprise more than 20% of patients enrolled in Part 2. All randomizations will be performed using an Interactive Web Response System (IWRS). ~~Patients enrolled in Part 2 will be stratified by peak work at baseline (>0.8 W/kg vs. ≤0.8 W/kg).~~	Treatment assignments for Part 2 clarified based on updated study design
Section 7.3 Treatment Assignment	Extension: All patients in the extension will be assigned to RTA 408 150 mg.	Added treatment assignments for the extension study

Section	Protocol Version 7	Rationale
Section 7.4.1 Selection of Doses	Part 1: ~~This 2-part study will evaluate~~ The safety, efficacy, and PD of RTA 408 at ~~several~~ multiple dose levels (2.5~~-mg~~, 5~~-mg~~, 10~~-mg~~, 20~~-mg~~, 40, 80, 160, and ~~higher doses (not to exceed~~ 300 mg~~)) in the treatment of patients with Friedreich's ataxia~~. will be evaluated in Part 1 to identify an appropriate dose for Part 2.	Language altered to reflect RTA 408 doses examined in Part 1
Section 7.4.1 Selection of Doses	~~PD data from the 2.5 mg cohort in Study 408-C-1303, an ongoing Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors, suggest that this may be in or near a pharmacologically active dose range based on an apparent induction of Nrf2 target genes in peripheral blood mononuclear cells after 28 days of treatment. This observation is consistent with the fact that plasma RTA 408 concentrations achieved at the 2.5 mg dose level are above those required for in vitro activation of Nrf2. Dose escalation by increments up to 100% increase from each prior cohort, to a maximum dose of 300 mg was selected as the highest potential dose in this study in an effort to adequately dose range and to provide good separation of treatment effects between dose groups. Doses from Part 1 will be evaluated for safety, efficacy, and PD to select two doses which appear to be pharmacologically active in patients with Friedreich's ataxia to be used) in Part 2.1 to identify an appropriate dose for Part 2.~~ ~~Based on the available safety data for RTA 408 in Friedreich's ataxia, mitochondrial myopathy, and oncology patients, the established independent DSMB overseeing safety, the well-characterized nonclinical safety findings, and the importance of appropriately evaluating the dose-response relationship and safety profile for RTA 408 in Friedreich's ataxia patients, Reata believes that evaluation of RTA 408 doses up to 300 mg is reasonable and the risk-benefit is acceptable. Specifically, a top dose of up to 300 mg is justified based on the following:~~	Removed justification for dose selection in Part 1
Section 7.4.1 Selection of Doses	~~• A 300 mg dose in humans is below the NOAEL identified in a 3-month monkey GLP toxicity study (based on mg/m2 dose or anticipated systemic exposure)~~ ~~• The relevant adverse findings observed in rats at lower doses than the 300 mg human dose were limited to the liver and kidney. To date, oral administration of RTA 408 to humans has not been associated with evidence of kidney or liver toxicity and we continue to carefully monitor patients at regular intervals for circulating markers of liver or kidney injury.~~ ~~• Reata believes that exploration of a broad dose range during Part 1 of this study, including clinical exposures up to approximately 1.94 hr*µg/mL, if possible, would afford the greatest likelihood of observing a maximally effective dose (assuming that safety data continue to support further dose escalation, determined by the DSMB and Sponsor)~~	Removed justification for dose selection in Part 1

Section	Protocol Version 7	Rationale
Section 7.4.1 Selection of Doses	Part 2 and Extension: No dose-limiting toxicity was observed in Part 1 and a dose of 150 mg was selected for Part 2. From the doses evaluated in Part 1, the 160 mg dose of RTA 408 was considered optimal based on DSMB and Sponsor assessment of available safety, efficacy, PK, and PD data. Available capsule strengths of RTA 408 (2.5-, 10-, and 50-mg capsules) require four capsules daily for a 160 mg dose and 3 capsules daily for a 150-mg dose. Available PK data from Part 1 demonstrate that systemic exposure to RTA 408 is reasonably linear with dose, with modest inter-subject variability (e.g., AUC CV% of approximately 14 to 40%). Consequently, a 150-mg dose, is anticipated to provide similar drug exposure as the 160-mg dose. Based on these considerations, an RTA 408 dose of 150 mg was selected for Part 2 because it differs by less than 10% from the 160-mg dose that was evaluated in Part 1 and therefore is expected to provide similar systemic exposure while affording a reduction in the number and complexity of capsules that patients are required to swallow once each day for 24 weeks during Part 2.	Added justification for 150 mg dose in Part 2
Section 7.4.2 Dose-Escalation Scheme	The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study~~, and the maximum permitted dose of RTA 408 is 300 mg.~~ (not to exceed 300 mg).	Language altered to reflect RTA 408 doses examined in Part 1
Section 7.4.2 Dose-Escalation Scheme	Part 2: Dose-escalation will not be used in Part 2. Patients randomized to RTA 408 will receive 150 mg of RTA 408 daily throughout the 24-week treatment period.	Clarification that no dose escalation will occur in Part 2
Section 7.4.2 Dose-Escalation Scheme	Extension: Dose-escalation or de-escalation will not be used in the extension portion of the study. Patients will receive 150 mg of RTA 408 daily throughout participation in the extension.	Clarification
Section 7.4.3 Criteria for Determining Dose-Limiting Toxicity	Part 1: For the purpose of intra-patient dose escalation in Cohort 1, the assessment of a DLT (i.e., a side effect serious enough to prevent an increase in dose) will be based on the clinical judgment of the investigator. ~~Within patient dose increases are only permitted for the first cohort of 8 patients. All other patients enrolled in the study will remain at a constant dose throughout the 12-week treatment period.~~ Suspected DLTs should be discussed with the medical monitor. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. All other patients enrolled in Part 1 will remain at a constant dose throughout the 12-week treatment period. Part 2 and Extension: Dose-escalation is not being used in Part 2 and side effects should be recorded as adverse events.	Clarification

Section	Protocol Version 7	Rationale
Section 7.4.5 Additional Considerations for Dose Escalation Decisions in Part 1	A maximum dose of 300 mg may be tested in Part 1 of this study	Clarification
Section 7.5 Data Safety Monitoring Board	A DSMB will review unblinded safety data throughout the study (i.e., Part 1, Part 2, and Extension) and make recommendations as appropriate.	Clarification
Section 7.5 Data Safety Monitoring Board	Part 2 and Extension data will be reviewed on a quarterly basis by the DSMB. After the last patient completes Part 2, the DSMB will determine if regular meetings are necessary or may convert to less frequent reviews to align better with the extension schedule of every 24 week visits	Added frequency of DSMB review in Part 2
Section 7.5 Data Safety Monitoring Board	A separate, blinded statistical group will be responsible for producing and finalizing the SAP and executing final data analysis for each part of the study.	Clarification that separate statistical analyses will be performed for Part 1 and Part 2
Section 7.5 Data Safety Monitoring Board	Briefly, the DSMB will review the progress of the study and the accumulating unblinded data while the study is ongoing. At each data review, the DSMB will assess safety, as evaluated by AEs, laboratory data (e.g., AST, ALT, bilirubin, alkaline phosphatase, magnesium, creatinine, BNP, etc.), limited functional assessment data (maximal exercise testing, ~~submaximal exercise testing, and FA rating scale~~ and mFARS score),	Clarification
Section 7.5 Data Safety Monitoring Board	In addition to the ~~monthly~~ reviews of unblinded study data, the DSMB will participate with the Sponsor in the recommendation to open the 10-mg cohort and ~~additional~~ higher dosing cohorts…	Clarification
Section 7.7 Schedule of Assessments	~~Schedules of assessments for Part 1 and Part 2 are listed individually in Appendix 1.~~	Removed Appendix with schedules of assessment for Part 1 and Part 2
Section 7.7 Schedule of Assessments	[e] Assessments for Visit 4 must be collected at the study center if patients are enrolled in Part 1 of the study. ~~If patients are enrolled in Part 2 of the study, Visit 4 assessments may be collected by a home health nurse.~~	Removed language discussing Part 2 of the study from Table 3

Section	Protocol Version 7	Rationale
Section 7.7 Schedule of Assessments	[m] Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic on Day 14, Day 56 (Cohort 1; Part 1 only) and Day 84 after the blood collection for predose PK analysis. All other doses can be administered at home. RTA 408 should be administered once daily through Day 84. ~~At Week 2, study drug dispensation is only required for patients in the first cohort of Part 1 of the study.~~	Clarification
Section 7.7 Schedule of Assessments	~~* For patients enrolled in Part 2 of the study, blood samples for PK analysis at Visit 5 and Visit 10 should be collected prior to study drug administration.~~	Clarification
Section 7.7 Schedule of Assessments	Table 4 and footnotes updated	Table 4 changed to reflect updated study design
Section 7.7 Schedule of Assessments	Fall diaries and activities of daily living added to Part 2 assessments	Table 4 changed to reflect updated study design
Section 7.7 Schedule of Assessments	Table 5 and footnotes added to reflect extension study design	Table 5 added to reflect updated study design
Section 8.1 Patient Inclusion Criteria (Part 1 and Part 2)	2. Have a modified FARS score ≥~~10 and ≤80~~ 20 and ≤80. The average of the two mFARS values collected at Screening and Day 1 visits must fall within the allowable range, and they must be within 4.5 points of each other	Increased lower bound of Modified FARS required for study entry and clarified that 2 consistent mFARS values are required for entry
Section 8.1 Patient Inclusion Criteria (Part 1 and Part 2)	7. Have a left ventricular ejection fraction ≥ 40% (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)	Echocardiograms for patient eligibility can be collected up to 90 days prior to Day 1

Section	Protocol Version 7	Rationale
Section 8.2 Patient Exclusion Criteria (Part 1 and Part 2)	3b. Pericardial constriction (based on echocardiogram performed at Screening Visit or within ~~30~~ 90 days prior to Screening Visit) 3c. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within ~~30~~ 90 days prior to Screening Visit)	Echocardiograms for patient eligibility can be collected up to 90 days prior to Day 1
Section 8.2 Patient Exclusion Criteria (Part 1 and Part 2)	6. Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than 1.5 times the upper limit of normal of ~~creatinine,~~ AST or ALT.	Clarification
Section 8.2 Patient Exclusion Criteria (Part 1 and Part 2)	7. Have any abnormal laboratory test value or ~~serious~~ clinically significant pre-existing medical condition that, in the opinion of the investigator, would put the patient at risk by study enrollment	Clarification
Section 8.2 Patient Exclusion Criteria (Part 1 and Part 2)	~~9d. Kidney insufficiency as defined by creatinine level >1.5 mg/dL~~	Clarification
Section 8.2 Patient Exclusion Criteria (Part 1 and Part 2)	20. Prior participation in a trial with RTA 408	Added that patients who previously participated in a trial with RTA 408 are not eligible to enroll
Section 8.3 Extension Eligibility	Patients must complete 12 weeks of treatment in Part 1, or 24 weeks of treatment in Part 2, have no major protocol deviations, and continue to meet inclusion and exclusion criteria as specified in Appendix 1.	Added extension eligibility criteria in Appendix 1
Section 8.4 Patient Rescreening	• Failed screening because of mFARS (the absolute difference in mFARS was ≥4.5 points between Screening and Day 1	Added that patients with high variability in Modified FARS between Screening and Day 1 may rescreen

Section	Protocol Version 7	Rationale
Section 8.5.1 Patient Discontinuation Criteria	Patients must permanently discontinue study drug if any of the following occur: · ALT or AST > 8X ULN; · ALT or AST > 5X ULN for more than 2 weeks; · ALT or AST > 3X ULN and total bilirubin > 2X ULN · ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). Patients who are discontinued from study drug in Part 1 or Part 2 should still complete all study visits and undergo all scheduled study assessments, if possible.	Added criteria for treatment discontinuation due to liver injury
Section 9.1 Description of Study Drug	Part 2: Patients will ingest 3 capsules daily throughout the study; study drug is described in Section 10.1. Treatment kits containing RTA 408 or placebo will include 3 bottles, each containing 30 count of either active (RTA 408 50 mg) or placebo capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.	Clarified dosing instructions for Part 2
Section 9.1 Description of Study Drug	Extension: Patients will ingest 3 capsules daily throughout the extension; study drug is described in Section 10.1. Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.	Added dosing instructions for extension study
Section 9.1.1 Management of Elevated Transaminase Levels (ALT and/or AST)	In ongoing clinical trials with RTA 408, transient increases in transaminases and GGT levels have been observed in some patients (refer to the Investigator's Brochure for additional information). Transaminases should be monitored using data from the scheduled lab draws in Part 2 of the study and should continue to be monitored in the extension following the patient's standard of care. Nearly all instances of elevated transaminases are expected to be asymptomatic. Transaminase levels (as well as total bilirubin [TBL], GGT, alkaline phosphatase) will be checked within 48 to 72 hours during an unscheduled visit if the following occurs: • ALT or AST levels > 3X ULN. Testing will be repeated every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week or until the patient withdraws consent.	Added guidance for managing elevated transaminases

Section	Protocol Version 7	Rationale
9.1.1 Management of Elevated Transaminase Levels (ALT and/or AST)	Study drug administration will be permanently discontinued if any of the following occurs: • ALT or AST > 8X ULN; • ALT or AST > 5X ULN for more than 2 weeks; • ALT or AST > 3X ULN and (TBL > 2X ULN); • ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). The hepatobiliary tree must be visualized (e.g., ultrasound, magnetic resonance imaging) and assessed if a patient discontinues taking study drug secondary to elevated transaminase levels. Additional tests/studies may be warranted depending on the clinical presentation.	Added guidance for managing elevated transaminases
Section 9.2.1 Excluded Medications	Patients who have taken any of the following drugs within 14 days prior to Study Day 1 will be excluded from ~~this study~~ Part 1 and Part 2:	Clarification
Section 9.2.1 Excluded Medications	The following medications and medication classes are not permitted during ~~this study~~ Part 1 and Part 2, except as noted in Section 9.2.2:	Clarification
Section 9.2.1 Excluded Medications	The following medications and medication classes are not permitted during the extension study • Sensitive substrates for cytochrome P450 2C8 or 3A4 (e.g., repaglinide, midazolam, sildenafil) • Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice) • Substrates for p-glycoprotein transporter (e.g., ambrisentan, digoxin)	Clarification
Section 9.2.2 Permitted Medications	The following concomitant medications are permitted only during the extension study: • Antioxidant supplements, including but not limited to idebenone, coenzyme Q10, nicotinamide, and dosages exceeding the recommended daily allowance of vitamin E • Anti-spasticity agents	Antioxidant supplements and anti-spasticity medication can be used during the Extension
Section 9.3 Compliance With Study Drug	All patients will return all bottles and unused pills ~~at the Weeks 4, 8, and 12 visits~~ and will be dispensed a new kit of study drug at ~~the Weeks 4 and 8~~ visits indicated in Table 3, Table 4, and Table 5.	Clarification
Section 9.3 Compliance With Study Drug	To be considered compliant with study drug, patients can miss no more than 25% of the total planned doses (i.e., 21 doses during Part 1 or 42 doses during Part 2) during the study	Clarification

Section	Protocol Version 7	Rationale
Section 9.4 Randomization	Patients enrolled in Part 1 cohorts will be randomized 3:1 to RTA 408 at the cohort -specific dose level or placebo. Patients enrolled in Part 2 will be randomized 1:1~~:1~~ to RTA 408 ~~at one of the two selected doses~~150 mg or placebo. Randomization in Part 2 will be stratified by pes cavus status (pes cavus vs. no pes cavus). Patients with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight-bearing, will not comprise more than 20% of patients enrolled in Part 2. Randomization for both Part 1 and Part 2 will be generated using a centralized IWRS. ~~Randomization for Part 2 will be stratified by peak work at baseline (> 0.8 W/kg vs. ≤ 0.8 W/kg).~~ Patients enrolled in the extension will be assigned to RTA 408 150 mg.	Updated randomization for Part 2 and extension study based on study design
Section 9.5 Blinding	The extension will be considered open-label. All patients in the extension will be assigned RTA 408 150 mg. Patients will not be unblinded to study treatment in Part 1 or Part 2 upon entering the extension study.	Clarification
Section 9.8 Treatment Interruption	Patients who are permanently discontinued from study drug during the extension should complete the end of study assessments, and be terminated from the study.	Clarification
Section 9.9 Study Procedures	All assessments occur in the study center clinic with the exception of those assessments for ~~Visits 3~~ (lab collection at Screening (all patients, Part 1 and Part 2) and ~~4 (patients in~~ Visit 3 (Part ~~2~~1 only), which may be performed by a home health visit nurse (at appropriate locations and approved by Sponsor) and those assessments for Visits 6 and 8 in Part 1 and Visits 3 and 6 in Part 2, which will be performed via telephone contact. Home health assessments are not permitted during the extension.	Updated study visits which may be performed by a home health study nurse
Section 9.9.2 Inclusion/Exclusion Criteria	Investigators and/or study site personnel should contact the medical monitor for any questions regarding patient eligibility.	Clarification
Section 9.9.3 Demographics and Baseline Disease Characteristics	Demographic data, including sex, age, race, and ethnicity, and baseline disease characteristics, including, but not limited to, documentation of genetic confirmation of Friedreich's ataxia and presence or absence of pes cavus, will be collected at the time indicated in Table 3 and Table 4.	Clarification
Section 9.9.4 Pes Cavus Assessment	The process for classifying pes cavus will be described in a separate study manual. Pes cavus will be assessed at the times indicated in Table 4 and Table 5. Patients who participated in Part 1 of the study must complete a pes cavus assessment at the Extension Study Screening visit (Table 5).	Added pes cavus assessment

Section	Protocol Version 7	Rationale
Section 9.9.8 Echocardiogram	For patients with echocardiograms collected within ~~30~~ 90 days prior to Screening Visit, the most recent echocardiogram can be used to assess cardiac function and patient eligibility.	Increased window in which Screening echocardiogram may be used for eligibility
Section 9.9.8 Echocardiogram	Patients from Part 1 of the study that want to participate in the Extension must have an echocardiogram collected within 90 days prior to Extension Day 1.	Clarification for patients from Part 1
Section 9.9.9 Electrocardiogram	An ECG is required for eligibility. If a patient has had an ECG completed within 90 days prior to the Screening Visit, the most recent ECG can be used as the screening assessment for patient eligibility.	Increased window in which Screening electrocardiogram may be used for eligibility
Table 8	Added leukocytes and nitrates to Urinalysis/Microscopy Assessments	Clarification
Section 9.9.22 Study Drug Return and Pill Count	Patients will be provided a dosing diary in Part 1 and Part 2 to track….	Clarification
Section 9.9.23 Study Drug Administration	Part 1: As outlined in Section 9.1, study drug treatment kits will contain up to six 30-count bottles of RTA 408 or placebo capsules. Patients should take 1 capsule from each bottle daily. Patients should self-administer study drug orally once daily in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). Study drug should be taken with water at the times indicated in Table 3, except on Days 1, 14, ~~28 (Part 2 only)~~, 56 (Cohort 1; Part 1 only), and 84, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, ~~28 (Part 2 only)~~, 56 (Cohort 1; Part 1 only), and 84. The date and time of the 2 most recent doses of study medication prior to Days 14, ~~28 (Part 2 only)~~, 56 (Cohort 1; Part 1 only), and 84 will be recorded for PK analysis. The date and time of the last study drug administration (Day 84) should be recorded. A vomited dose should not be replaced. Missed doses may be taken in the afternoon or evening of the same day approximately 1 hour before or 2 hours after a meal. A double dose (e.g., missed dose from previous day and dose for current day) should not be taken.	Added study drug administration instructions for Part 1 only

Section	Protocol Version 7	Rationale
Section 9.9.23 Study Drug Administration	Part 2: As outlined in Section 9.1, study drug treatment kits will contain three 30-count bottles of RTA 408 or placebo capsules. Patients should self-administer study drug orally once daily in the morning on an empty stomach (approximately 1 hour before or 2 hours after eating). Study drug should be taken with water at the times indicated in Table 4, except on Days 1, 14, 84, and 168, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, 84 and 168. The date and time of the 2 most recent doses of study medication prior to Days 14, 84 and 168 will be recorded for PK analysis. The date and time of the last study drug administration (Day 168) should be recorded.	Added study drug administration instructions for Part 2
Section 9.9.23 Study Drug Administration	Extension: As outlined in Section 9.1, patients will ingest 3 capsules daily throughout the study. Study drug should be taken with water at the times indicated in Table 5. Treatment kits containing RTA 408 will include 3 bottles, each containing 30 count of active (RTA 408 50 mg) capsules. Patients may receive more than 1 treatment kit during dispensation to provide sufficient study drug until their next planned dispensation.	Added study drug administration instructions for extension study
Section 9.9.25 Maximal Exercise Test	On study days where multiple assessments are to be completed, the maximal exercise test must be the first functional assessment performed.	Clarification
Section 9.9.26 Friedreich's Ataxia Rating Scale	The examiner will complete the full FARS neurological examination on the patient at the times indicated in Table 3 and Table 4 and Table 5. A practice FARS assessment is included in the schedule of assessments to familiarize those patients who have not recently completed a FARS assessment with the components of the neurological exam. The practice FARS assessment is not required for patients having completed a FARS assessment within 90 days prior to Screening. The practice FARS assessment must be performed prior to the screening maximal exercise test. Other than the practice FARS, all FARS neurological examinations must be performed following maximal exercise testing. The examiner will need a reflex hammer, tuning fork, and stopwatch.. Instructions will be provided in the study manual. The FARS examination should be completed by one of the neurologists ~~or trained physician~~ at the site delegated to complete this assessment.	Clarification
Section 9.9.26 Friedreich's Ataxia Rating Scale	The ~~modified~~ full neurologic FARS is divided into ~~4~~ 5 sections: bulbar, upper limb coordination, lower limb coordination, peripheral nervous system, and upright stability.	Clarification

Section	Protocol Version 7	Rationale
Section 9.9.26 Friedreich's Ataxia Rating Scale	The modified FARS ~~consists of only the neurological portion of~~ is not a separate assessment, but rather calculated as the full FARS neurological assessment, minus section D (peripheral nervous system). The modified FARS includes into 4 sections: bulbar, upper limb coordination, lower limb coordination, and upright stability.	Clarification
Section 9.9.30 Activities of Daily Living	Patients will be instructed to answer the 9 questions on the Activities of Daily Living survey at the times indicated in Table 4 and Table 5. The Activities of Daily Living survey (Appendix 4) assesses 9 concepts: (1) speech; (2) swallowing; (3) cutting food and handling utensils; (4) dressing; (5) personal hygiene; (6) falling; (7) walking; (8) quality of sitting position; and (9) bladder function.	Addition for Part 2
Section 9.9.31 Falls Diary	Throughout Part 2 of the study, patients will be instructed to record any instances of falls in a study diary (Table 4). A fall is defined as "the patient unintentionally coming to rest on the ground or at a lower level." Items included on the falls diary may include but are not limited to the date and time of each fall, the location of the fall, the preceding activity prior to the fall, the perceived cause of the fall, and if an injury was sustained after the fall. Patients will be provided the fall diary at Screening and must record fall incidents between Screening and Week 24.	Addition for Part 2
Section 9.9.33 Home Health Visits	Patients at approved sites will have the option of having a home health visit at the Screening Visit (all patients, Part 1 and Part 2) and Visit 3 (Part 1 only).	Clarification
Table 9	Manufacturer deleted from table	Manufacturer deleted from table
Section 10.2 Study Drug Packaging and Labeling	Treatment kits containing ~~up to~~ three, four, or six bottles, depending on treatment assignment…	Study packaging updated to reflect different kit designs
Section 10.2 Study Drug Packaging and Labeling	Contents: One bottle containing 30 capsules of either RTA 408 or matching placebo. Bottle also contains one desiccant insert, which should not be ingested	Clarification
Section 11.2 Part 2	Efficacy assessments for Part 2 included in separate section	Clarification
Section 11.2.1 Friedreich's Ataxia Rating Scale	The change in both the FARS neurological score and the modified FARS scores from Baseline to Weeks 4, 12, 18, and 24 will be analyzed.	Clarification for Part 2

Section	Protocol Version 7	Rationale
Section 11.2.2 Maximal Exercise Test	The changes in peak work and oxygen utilization during maximal exercise testing from Baseline to Weeks 4, 12, 18, and 24 will be analyzed.	Clarification for Part 2
Section 11.2.3 9-Hole Peg Test	The change in performance on the 9-HPT from Baseline to Week 24 will be analyzed.	Clarification for Part 2
Section 11.2.4 25-Foot Timed Walk Test	The change in performance on the 25-foot timed walk test from Baseline to Week 24 will be analyzed.	Clarification for Part 2
Section 11.2.5 SF-36 Health Survey Update	The change in SF-36 patient-reported outcome scores from Baseline to Week 24 will be analyzed.	Clarification for Part 2
Section 11.2.6 Activities of Daily Living	The change in activities of daily living from Baseline to Week 24 will be analyzed	Clarification for Part 2
Section 11.2.5 Frequency of Falls	The frequency of falls from Screening through Week 24 will be analyzed.	Clarification for Part 2
Section 12.1 Safety Parameters	Safety parameters in Part 1 and Part 2 include results of echocardiogram, ECG, vital sign measurements, weight, BMI, physical examination, AEs, SAEs, concomitant medications, and laboratory tests (clinical chemistry, hematology, urinalysis, microscopy, assessment of BNP and NT-Pro BNP, and pregnancy tests [as indicated]). Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and assessment of BNP and NT-Pro BNP.	Added safety parameters for extension study
Section 12.2.1.1 Adverse Event	Pre-planned elective procedures (surgeries or therapies) that are performed to manage/treat conditions that existed prior to the patient's enrolling in the trial (e.g., elective periodontal surgery, elective hernia repair) should not be recorded as AEs, but should be documented in the patient's source documents. If a pre-planned procedure is performed early (e.g., as an emergency) because the pre-existing condition worsens, the worsening condition should be captured as an AE.	Clarification

Section	Protocol Version 7	Rationale
Table 10	[redacted] MD ~~Trial Runners, LLC~~ Reata Pharmaceuticals, Inc ~~128 W. Villared~~ 2801 Gateway Drive, Suite 150 ~~Dickinson, ND 58601 USA~~ Irving, TX 75063 Office: [redacted] Mobile: [redacted] Email: [redacted]	Change in medical monitor
Section 14.1 Sample Size	Part 1: ~~With 24 patients enrolled in Part 2 (8 patients per treatment cohort), this study has approximately 80% power to detect an improvement of 0.28 W/kg in the peak work of pooled RTA 408 (n=16) versus placebo (n=8) assuming a two-sided Type I error rate of 0.05, a common within-group standard deviation (SD) of 0.28 W/kg, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group. The analysis will use repeated measures methodology, assuming compound symmetry for the within subject covariance structure (ρ=0.20).~~	Removed previous language regarding power calculations and sample size for Part 2
Section 14.1 Sample Size	Part 2: ~~14.1.1. Sample Size Recalculation~~ ~~A sample size recalculation will be performed in Part 2 after all 24 patients have been randomized to evaluate the pooled distribution of baseline peak work. If the SD for pooled, baseline peak work is greater than 0.28 W/kg or the distribution is not approximately normal, then an additional 12 patients will be enrolled in Part 2. With 36 patients enrolled in Part 2 (i.e., 12 patients per randomized treatment cohort), the 80% power is retained to detect the same difference of 0.28 W/kg if the SD is up to 0.35 W/kg, under the same assumptions of a two-sided Type I error rate of 0.05, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group, assuming compound symmetry for the within-subject covariance structure (ρ=0.20).~~	Removed previous language regarding sample size recalculation for Part 2

Section	Protocol Version 7	Rationale
Section 14.1 Sample Size	[redacted] Since Part 1 and Part 2 are independent sets of patients, the Part 1 analysis will not impact the type I error rate for the Part 2 analysis.	Updated power and sample size for Part 2
Section 14.1 Sample Size	Extension: The sample size for the extension is limited to the number of patients having completed Part 1 or Part 2.	Addition
Section 14.2.3 Efficacy Variables	Part 2: Efficacy variables are modified FARS scores, full FARS scores, peak work during maximal exercise testing, parameters collected during maximal exercise testing, FARS score, 9-HPT scores, 25-foot timed walk test distance, ADL, and SF-36 scores.	Added efficacy variables specific to Part 2
Section 14.2.4 Safety Variables	The safety variables in Part 1 and Part 2 include results of echocardiogram, ECGs, weight and BMI, vital sign measurements, physical examinations, laboratory test results (clinical chemistry, hematology, urinalysis, microscopy, and pregnancy tests [as indicated]), concomitant medications, AEs, and SAEs. Safety parameters in the extension study include vital sign measurements, physical examination results, AEs, SAEs, weight, and assessment of BNP and NT-Pro BNP. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and analyses of the AE data will be detailed in the SAP.	Added safety parameters in extension study
Section 14.3 Statistical Analyses	Separate SAPs will be written for each study part. The SAPs will detail the analyses to be performed for each study part and will be developed prior to the database lock of each study part.	Clarification that Part 1 and Part 2 statistical analysis plans will be separate

Section	Protocol Version 7	Rationale
Section 14.3.1 Analysis Sets	Part 1 and Part 2 will be analyzed separately. For Part 1 and Part 2, the following analysis sets will be defined: • The intent-to-treat (ITT) population includes all enrolled patients ~~in both study parts (i.e., Part 1 and Part 2)~~ categorized by their assigned treatment group (whether or not they received study drug). ~~• The modified ITT (mITT) population includes all patients enrolled in Part 2 of the study categorized by their assigned treatment group (whether or not they received study drug). Efficacy analyses will be performed using the mITT population.~~	Clarification to analysis sets based on separate statistical analysis plans for Part 1 and Part 2
Section 14.3.1 Analysis Sets	Extension: All patients who received at least 1 dose of study drug in the extension will be included in the extension safety population.	Addition for extension
Section 14.3.2 Primary Efficacy Analysis	Primary analysis of the efficacy data will be based on the ~~mITT~~ ITT population, ~~which will include all patients randomized in Part 2 of the study. Peak work from Part 2 for the pooled patients treated with RTA 408 will be compared with placebo after 12 weeks of treatment by.~~ Mixed-model repeated measures (MMRM) analysis ~~of covariance, with treatment group, time~~ will be used to analyze the Part 1 and Part 2 primary and secondary efficacy objectives. All scheduled efficacy values collected through the end of the treatment visit (i.e., Week 12 Part 1, Week 24 Part 2) will contribute to the primary analysis. The primary analyses of efficacy with MMRM are expected to be at least as powerful as the 2-sided t-test calculations used for study planning.	Added description of repeated measures for primary efficacy analysis
Section 14.3.2 Primary Efficacy Analysis	The dependent variable will be change from baseline. The model may include treatment, visit, and the interaction between treatment and ~~time~~visit as fixed ~~factors~~effects; and ~~baseline peak work~~visit will serve as a ~~covariate. The difference between RTA 408 and placebo in change from baseline of mean peak work will be estimated along with the 95% confidence interval of the difference.~~repeated measure. The SAP will ~~describe~~specify the ~~strategy used to control~~choice of variance-covariance structure and may specify additional covariates. The SAP may specify additional covariates. Procedures for handling missing data and appropriate sensitivity analyses will be described in the ~~Type I error rate when comparing~~SAP for each ~~dose~~study part.	Added description of repeated measures for primary efficacy analysis

Section	Protocol Version 7	Rationale
Section 14.3.2 Primary Efficacy Analysis	Extension analysis of safety: As the extension is of an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (i.e., RTA 408 ~~with~~ or placebo).	Clarification
Section 15.1 Study Monitoring	The Sponsor or its designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6(~~R1~~R2), abbreviated as ICH E6(~~R1~~R2), and current standard operating procedures.	Clarification
Section 17.2 Ethical Conduct of the Study	The principal investigator agrees to conduct the study in accordance with the International Conference on Harmonization (ICH) for Guidance for Industry on GCP ICH E6(R1) and the principles of the Declaration of Helsinki [http://www.wma.net/en/30publications/10policies/b3/].	Clarification
Appendix 1	Appendix 1 added to specify eligibility criteria for the extension study	Addition



AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 408-C-1402
A PHASE 2 STUDY OF THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF RTA 408 IN THE TREATMENT OF FRIEDREICH'S ATAXIA

Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015
Version 05	29 September 2015
Version 06	23 May 2016

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Reata Pharmaceuticals, Inc. Any unauthorized use or disclosure of such information without the prior written authorization of Reata Pharmaceuticals, Inc. is expressly prohibited.

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 5 to produce the text of Version 6. Additionally, the following points are provided.

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strike through~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis have not been described.
- Section numbers refer to the numbers in the new version of the protocol.
- Grammatical corrections and minor editorial changes are not described.

Section	Protocol Version 6	Rationale
Sponsor Approval and Signature Page	[redacted]	Change in Clinical Operations Director
Table 1	[redacted] [redacted] MS, [redacted] Reata Pharmaceuticals, Inc. 2801 Gateway Drive, Suite 150 Irving, TX 75063 Office: [redacted] Mobile: [redacted] Email: [redacted]	Staffing change
Synopsis Studied Period	Estimated date last patient completed: December ~~2016~~ 2017	Extended study duration based on modifications to study design
Section 7.1 Overall Study Design	Part 1: The first part of the study will be a randomized, placebo-controlled, double-blind, dose-ranging study to evaluate the safety, efficacy, and pharmacodynamic (PD) activity of RTA 408 at 2.5 mg, 5 mg, 10 mg, 20 mg, and higher dose levels (not to exceed ~~160~~ 300 mg) in patients with Friedreich's ataxia. A cohort consists of the next eight eligible patients randomized 3:1 to RTA 408 at the cohort specific dose (n=6) or placebo (n=2). ~~Approximately 8~~ Up to and approximately 9 cohorts will be enrolled in Part 1 to allow for adequate dose-ranging for selection of two doses of RTA 408 to be used in Part 2.	Modify Part 1 of the study to allow for up to 9 cohorts and a maximum RTA 408 dose of 300 mg
Section 7.1 Overall Study Design	The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is ~~160~~300 mg.	Modify Part 1 of the study to allow for a maximum RTA 408 dose of 300 mg

Section	Protocol Version 6	Rationale
Section 7.1 Overall Study Design	Once ~~doses are selected for~~ enrollment begins in Part 2 ~~by the Sponsor~~, no additional cohorts will be enrolled in Part 1.	Clarification
Figure 1	Modified to reflect changes in study design	Modify Part 1 of the study to allow for up to 9 cohorts and a maximum RTA 408 dose of 300 mg
Section 7.2 Number of Patients	~~Approximately 100~~ Up to approximately 108	Clarification
Section 7.4.1 Selection of Doses	This 2-part study will evaluate the safety, efficacy, and PD of RTA 408 at several dose levels (2.5 mg, 5 mg, 10 mg, 20 mg, and higher doses (not to exceed ~~160~~ 300 mg) in the treatment of patients with Friedreich's ataxia.	Modify Part 1 of the study to allow for a maximum RTA 408 dose of 300 mg
Section 7.4.1 Selection of Doses	Dose escalation by increments up to 100% increase from each prior cohort, to a maximum dose of ~~160~~ 300 mg was selected as the highest potential dose in this study in an effort to adequately dose range and to provide good separation of treatment effects between dose groups.	Modify Part 1 of the study to allow for a maximum RTA 408 dose of 300 mg

Section	Protocol Version 6	Rationale
Section 7.4.1 Selection of Doses	Based on the available safety data for RTA 408 in Friedreich's ataxia, mitochondrial myopathy, and oncology patients, the established independent DSMB overseeing safety, the well-characterized nonclinical safety findings, and the importance of appropriately evaluating the dose-response relationship and safety profile for RTA 408 in Friedreich's ataxia patients, Reata believes that evaluation of RTA 408 doses up to 300 mg is reasonable and the risk-benefit is acceptable. Specifically, a top dose of up to 300 mg is justified based on the following: • A 300-mg dose in humans is below the NOAEL identified in a 3-month monkey GLP toxicity study (based on mg/m^2 dose or anticipated systemic exposure) • The relevant adverse findings observed in rats at lower doses than the 300-mg human dose were limited to the liver and kidney. To date, oral administration of RTA 408 to humans has not been associated with evidence of kidney or liver toxicity and we continue to carefully monitor patients at regular intervals for circulating markers of liver or kidney injury. • Reata believes that exploration of a broad dose range during Part 1 of this study, including clinical exposures up to approximately 1.94 hr*µg/mL, if possible, would afford the greatest likelihood of observing a maximally effective dose (assuming that safety data continue to support further dose escalation, determined by the DSMB and Sponsor).	Added detail surrounding rationale for dose selection
Section 7.4.2 Dose-Escalation Scheme	The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is ~~160~~ 300 mg.	Modify Part 1 of the study to allow for a maximum RTA 408 dose of 300 mg
Section 7.4.3 Criteria for Determining Dose-Limiting Toxicity	Within patient dose increases are only permitted for the first cohort of 8 patients. All other patients enrolled in the study will remain at a constant dose throughout the 12-week treatment period.	Clarification

Section	Protocol Version 6	Rationale
Section 7.4.5 Additional Considerations for Dose Escalation Decisions	A maximum dose of 300 mg may be tested in this study; however, each dose escalation is limited to a 100% increase from the previous dose. If the Sponsor or DSMB considers dose escalation not safe for any reason, no more dose escalation will be carried out. The DSMB may recommend stopping dose escalation at any time, particularly if their review of AEs or laboratory data (e.g., AST, ALT, bilirubin, alkaline phosphatase, magnesium, creatinine, BNP, etc.), reveals any potential safety concern. The Sponsor, in addition to reviewing all available safety and efficacy data, will also take into consideration the predicted systemic exposure to RTA 408 at the next proposed dose in comparison with the exposure vs adverse effect profile for RTA 408 in animals. If systemic exposure is sufficiently high to warrant a potential concern based on animal toxicity data, dose escalation may be stopped or paused, if needed, to seek additional input from the DSMB or FDA.	Added detail surrounding rationale for dose escalation criteria
Section 7.5 Data Safety Monitoring Board	At each data review, the DSMB will assess safety, as evaluated by AEs, laboratory data (e.g., AST, ALT, bilirubin, alkaline phosphatase, magnesium, creatinine, BNP, etc.), limited functional assessment data (maximal exercise testing, submaximal exercise testing, and FA rating scale score), and changes in other laboratory and vital sign parameters. The DSMB will assess whether the study should be stopped for safety concerns or the informed consent updated to include new safety information. In addition, the DSMB will review SAEs from the safety database, including narratives.	Added detail surrounding safety assessments
Section 9.1 Description of Study Drug	Depending on cohort dose level (or doses selected for part 2) patients will ~~ingest either 3 or 4~~ up to 6 capsules of study drug (1 from each bottle included in study treatment kit) daily throughout the study; study drug is described in Section 10.1. Treatment kits containing up to ~~30~~ 160 mg of RTA 408 or placebo will include ~~three~~ 4 bottles, each containing 30 count of either active or placebo capsules. Treatment kits containing greater than ~~30~~ 160 mg of RTA 408 or placebo will be comprised of ~~four~~ 6 bottles, each containing 30 count of either active or placebo capsules.	Changes to kit design due to amended study design
Section 9.9.21 Study Drug Administration	As outlined in Section 9.1, study drug treatment kits will contain ~~either three or four~~ up to six	Changes to kit design due to amended study design

Section	Protocol Version 6	Rationale
Section 10.2 Study Drug Packaging and Labeling	Treatment kits containing ~~either three or four~~ up to six bottles…	Changes to kit design due to amended study design



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Version 05	29 September 2015

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SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 4 to produce the text of Version 5. Additionally, the following points are provided.

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strike through~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis have not been described.
- Section numbers refer to the numbers in the new version of the protocol.
- Grammatical corrections and minor editorial changes are not described.

Section	Protocol Version 5	Rationale
Global	Estimated date last patient completed: ~~June~~December 2016	Update study duration due to additional cohorts included in Part 1 of the study.
Section 7.1 Overall Study Design	The first part of ~~this~~the study will be a randomized, placebo-controlled, double-blind, dose ~~escalation~~ranging study to evaluate the safety, efficacy, and pharmacodynamic (PD) activity of RTA 408 at 2.5 mg, 5 mg, 10 mg, 20 mg, and ~~up to two additional~~higher dose levels in patients with Friedreich's ataxia. ~~An initial~~A cohort consists of ~~8~~ the next eight eligible patients ~~will be~~ randomized 3:1 to RTA 408 ~~2.5 mg~~ at the cohort specific dose (n=6) or placebo (n=2). Approximately 8 cohorts will be enrolled in Part 1 of the study to allow for adequate dose-ranging for selection of two doses of RTA 408 to be used in Part 2.	Modify Part 1 of the study to allow for up to 8 cohorts.

Section	Protocol Version 5	Rationale
Section 7.1 Overall Study Design	Intra-patient dose-escalation will only be utilized in the first cohort to evaluate RTA 408 at the first two dose levels (2.5 mg and 5 mg). Patients enrolling in the first cohort will be randomized to RTA 408 2.5 mg or placebo. After the Week 2 visit, each patient in the first cohort will dose -escalate ~~starting~~ to 5 mg (or remain on placebo) on Day 15 unless a dose-limiting toxicity (DLT) is reported in that patient (Section 7.4.3). ~~Patients originally randomized to RTA 408 2.5 mg will dose escalate to RTA 408 5 mg, and those randomized to placebo will continue on placebo in a blinded fashion.~~ After the last patient in the first cohort completes their Week 4 visit (i.e., 2 weeks on 2.5 mg daily [or matching placebo] followed by 2 weeks on 5 mg daily [or matching placebo]), the data safety monitoring board (DSMB) and Sponsor will review all available safety information and make a decision regarding enrollment of the next cohort. ~~If the 10 mg cohort is opened for enrollment, an additional 8 patients will be randomized 3:1 to RTA 408 10 mg or placebo. After the last patient in the 10-mg cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information and make a decision regarding enrollment of an additional dosing cohort or continuation to Part 2 of the study. Up to two additional cohorts may be added in Part 1 of the study, based on recommendation from the DSMB and Sponsor data review. If a third cohort (i.e., first additional cohort) is opened for enrollment, 8 new patients will be randomized 3:1 to RTA 408 (at a dosage strength that does not exceed 100% dose escalation from the second cohort) or placebo. After the last patient in the third cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information and make a decision regarding enrollment of the second additional (fourth) dosing cohort (at a dosage strength that does not exceed 100% dose escalation from the third cohort), following the same process described for the first additional cohort, or continuation to Part 2 of the study.~~	Condensed the description of each dosing cohort within Part 1 of the study.

Section	Protocol Version 5	Rationale
Section 7.1 Overall Study Design	~~Increases of no more than 100% from the prior RTA 408 dose level will be permitted in the additional dose-escalation cohorts. The dose specified in the DSMB recommendation will be considered the highest potential next dose based on review of safety data. The sponsor will review available data and select the dose for each additional cohort no higher than the DSMB recommended dose. Review of data for safety, dose escalation, and continuation to Part 2 are guided by the dose-escalation scheme in Section 7.4.2.~~Beginning with the second 8-patient cohort, once the eighth patient enrolled completes their Week 2 visit, the DSMB will review all available safety information and recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is 160 mg. The dose level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data. Prior to opening each cohort in Part 1 for enrollment, the Sponsor will evaluate all available data from doses studied in Part 1 to determine if enough information is available to select doses for Part 2 of the study. Once doses are selected for Part 2 by the Sponsor, no additional cohorts will be enrolled in Part 1.	Modified the description of each dosing cohort and specified that the maximum RTA 408 dose for this study will be 160 mg.
Section 7.2 Number of Patients	~~Up to 68~~ Approximately 100 patients will be enrolled in this study.	Number of patients increased with the addition of more cohorts in Part 1.
Section 7.3 Treatment Assignment	Patients enrolled in the first cohort for Part 1 will be randomized 3:1 to receive RTA 408 2.5 mg or placebo. After the Week 2 visit, patients receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg starting on Day 15 unless a DLT is observed. ~~Patients enrolled~~ Intra-patient dose-escalation will only be utilized in the first cohort for Part 1. Starting with the second cohort for Part 1, patients will be randomized 3:1 to receive the cohort specific dose level of RTA 408 ~~10 mg~~ or placebo. ~~Patients enrolled in the third cohort in Part 1 will be randomized 3:1 to receive RTA~~ and will remain on the same treatment assignment throughout the study.	Clarification that cohorts 2 through 8 will be randomized to a cohort-specific dose or placebo.

Section	Protocol Version 5	Rationale
Section 7.3 Treatment Assignment	Two dose levels of RTA 408 (~~at a dosage strength that does not exceed 100% dose escalation from the second cohort) or placebo.~~ evaluated in Part 1 will be used in Part 2. Patients enrolled ~~in the fourth cohort in Part 1 will be randomized 3:1 to receive RTA 408 (at a dosage strength that does not exceed 100% dose escalation from the third cohort) or placebo. Patients enrolled in~~ Part 2 of the study will be randomized 1:1:1 to ~~one of 2 dose levels of~~ RTA 408 ~~selected from Part 1~~ low dose, RTA 408 high dose, or placebo.	Clarification that two dose levels of RTA 408 and placebo will be used in Part 2.
Section 7.4.1 Selection of Doses	This 2-part study will evaluate the safety, efficacy, and PD of RTA 408 at several dose levels (2.5 mg, 5 mg, 10 mg, 20 mg, and ~~two additional dose levels~~ higher doses (not ~~exceeding 100% dose escalation from the prior dose level)~~to exceed 160 mg) in the treatment of patients with Friedreich's ataxia. PD data from the 2.5-mg cohort in Study 408-C-1303, an ongoing Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors, suggest that this may be in or near a pharmacologically active dose range based on an apparent induction of Nrf2 target genes in peripheral blood mononuclear cells after 28 days of treatment. This observation is consistent with the fact that plasma RTA 408 concentrations achieved at the 2.5 mg dose level are above those required for in vitro activation of Nrf2. Dose escalation by increments up to 100% increase from the ~~third~~ each prior cohort, to a maximum dose of 160 mg was selected as the highest potential dose in this study in an effort to adequately dose range and to provide good separation of treatment effects between dose groups. Doses from Part 1 will be evaluated for safety, efficacy, and PD to select two doses which appear to be pharmacologically active in patients with Friedreich's ataxia to be used in Part 2.	Updated dose levels in Part 1 and clarification regarding dose selection in Part 2.

Section	Protocol Version 5	Rationale
Section 7.4.2 Dose-Escalation Scheme	In Part 1 of the study, an initial cohort of 8 patients will be randomized 3:1 to RTA 408 2.5 mg (n=6) or placebo (n=2). Each patient in the first cohort will be evaluated for ~~intrapatient~~ intra-patient dose escalation by their investigator at the Week 2 visit. If no DLTs are observed by Week 2 for that patient, the patient will dose escalate. The patients receiving RTA 408 2.5 mg will begin receiving RTA 408 5 mg on Day 15 and the patients receiving placebo will remain on placebo in a blinded fashion. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. Patients who are deemed inappropriate for dose escalation will continue on their originally randomized dose (i.e., 2.5 mg or placebo) throughout the remainder of the study. After the last patient in the initial cohort completes their Week 4 visit, the DSMB and Sponsor will review all available safety information from this cohort and make a recommendation regarding opening the next cohort to be randomized 3:1 to ~~RTA 408 10 mg (n=6) or placebo (n=2). After the last patient in the 10 mg cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information to determine if an additional (third) cohort of RTA 408 up to 100% dose escalation (n=6) or placebo (n=2) may be added. After the last patient in the third cohort completes their Week 2 visit, the DSMB and Sponsor will review available data to determine if an additional (fourth) cohort of RTA 408 up to 100% dose escalation (n=6) or placebo (n=2) may be added. After the last patient in the final cohort of Part 1 completes their Week 2 visit, the DSMB and Sponsor will review available safety information to make a decision regarding continuation to study Part 2.~~the cohort specific dose level of RTA 408 or placebo. All subsequent cohorts in Part 1, beginning with the second 8-patient cohort, will be evaluated for safety of the cohort specific dose level by the DSMB once the eighth patient enrolled completes their Week 2 visit. The DSMB will recommend the dose of RTA 408 for the subsequent cohort. The DSMB dose recommendation for each cohort must not exceed 100% more than the highest dose of RTA 408 previously evaluated in this study, and the maximum permitted dose of RTA 408 is 160 mg. The dose level for each new cohort will not exceed the DSMB recommended dose level, and it will be selected by the Sponsor based on review of available safety, efficacy, PK, and PD data.	Clarification of randomization in Part 1 for additional cohorts.

Section	Protocol Version 5	Rationale
Section 7.5 Data Safety Monitoring Boar	In addition to the monthly reviews of unblinded study data, the DSMB will participate with the Sponsor in the recommendation to open the 10-mg cohort and ~~up to two~~ additional dosing cohorts	Clarification
Section 8.2 Exclusion Criteria	19. Be pregnant or breastfeeding	Additional exclusion criteria added for clarity.
Section 9.4 Randomization	~~The first cohort~~ Patients enrolled in Part 1 cohorts will be randomized 3:1 to RTA 408 ~~2.5 mg~~ at the cohort specific dose level or placebo. ~~The second cohort~~Patients enrolled in Part ~~1~~2 will be randomized ~~3~~1:1:1 to RTA 408 ~~10 mg or placebo. Subsequent Part 1 cohorts will be randomized in the same ratio. Patients enrolled in Part 2 will be randomized 1:1:1 to RTA~~ at one of the two selected doses or placebo. Randomization for both Part 1 and Part 2 will be generated using a centralized IWRS. Randomization for Part 2 will be stratified by peak work at baseline (> 0.8 W/kg vs. ≤ 0.8 W/kg).	Clarification of randomization in Part 1 for additional cohorts.
Section 9.9.25 Friedreich's Ataxia Rating Scale	The FARS examination should be completed by one of the neurologists or trained physician at the site delegated to complete this assessment.	Clarification
Section 9.9.26 25-Foot Timed Walk Test	~~The 25-foot timed walk test will be performed as part of the modified FARS.~~	Clarification. The 25-foot timed walk test is not included in the FARS.
Section 10.1 Study Drug	Capsules containing ~~either~~ RTA 408 ~~drug product, in~~ at the 2.5-mg, 10-mg, and ~~10~~50-mg strengths, or ~~placebo~~ the corresponding placebos, as described in Table 7 will be used in this study.	Updated to allow for use of 50-mg capsules.

Section	Protocol Version 5	Rationale
Table 7	RTA 408 Capsule, 2.5 mg, 10 mg, 50 mg	Updated to allow for use of 50-mg capsules.
Section 10.2 Study Drug Packaging and Labeling	Additionally, expiry information will be provided on treatment kits intended for use in the EU.	Clarification for potential sites outside of the US.
Table 8	~~Email:~~ [redacted] Email: [redacted] [redacted] SAE Hotline: [redacted] Safety Fax: [redacted]	Updated Medpace international reporting information.
Section 14.1 Sample Size	The sample size for Part 1 is based on a dose-escalation scheme to evaluate initial safety, PK, and PD activity of RTA 408 in this patient population. The small number of patients at each dose in Part 1 is not expected to fully characterize safety, efficacy, or PD, but rather inform the DSMB and Sponsor of the appropriate doses to select for Part 2.	Clarification



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Protocol History

Version 01	23 July 2014
Version 02	11 September 2014
Version 03	13 October 2014
Version 04	12 May 2015

Confidentiality Statement

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SUMMARY OF CHANGES

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Section	Protocol Version 4	Rationale
Global	Up to ~~7~~ 10 study centers	Enrollment of up to 2 additional cohorts in Part 1 may require more sites.
Section 7.1 Overall Study Design	The first part of this study will be a randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg, 5 mg, ~~and~~ 10 mg, and up to two additional dose levels) in patients with Friedreich's ataxia.	Modify Part 1 of the study to allow for up to 2 additional cohorts of patients.
Section 7.1 Overall Study Design	After the last patient ~~randomized to RTA 408~~ in the 10-mg ~~or placebo~~ cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information and ~~to~~ make a decision regarding enrollment of an additional dosing cohort or continuation to Part 2 of the study. Up to two additional cohorts may be added in Part 1 of the study, based on recommendation from the DSMB and Sponsor data review. If a third cohort (i.e., first additional cohort) is opened for enrollment, 8 new patients will be randomized 3:1 to RTA 408 (at a dosage strength that does not exceed 100% dose escalation from the second cohort) or placebo. After the last patient in the third cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information and make a decision regarding enrollment of the second additional (fourth) dosing cohort (at a dosage strength that does not exceed 100% dose escalation from the third cohort), following the same process described for the first additional cohort, or continuation to Part 2 of the study. Increases of no more than 100% from the prior RTA 408 dose level will be permitted in the additional dose-escalation cohorts. The dose specified in the DSMB recommendation will be considered the highest next dose based on review of safety data. The sponsor will review available data and select the dose for each additional cohort no higher than the DSMB recommended dose. Review of data for safety, dose escalation, and continuation to Part 2 are guided by the dose-escalation scheme in Section 7.4.2. ~~All patients in Part 1 will continue taking study drug for a total of 12 weeks.~~	Modify Part 1 of the study design to allow for up to 2 additional cohorts of patients.

Section	Protocol Version 4	Rationale
Section 7.1 Overall Study Design	Part 2: The second part of this study will be a randomized, placebo-controlled, double-blind, parallel study to evaluate the safety, efficacy, and PD of ~~up to~~ 2 dose levels of RTA 408 in patients with Friedreich's ataxia. Assuming that ~~the 2.5 mg, 5 mg, and 10 mg~~ doses tested in Part 1 have been deemed acceptable in ~~Part 1~~ the first part of the study, the first 24 eligible patients in Part 2 will be randomized 1:1:1 to receive RTA 408 ~~2.5 mg, RTA 408 10 mg~~ at the selected doses, or placebo (n=8 per treatment group). The two doses to be selected are based on DSMB and Sponsor review of data from Part 1, including available safety and PK data.	Modify Part 2 to allow the 2 doses of RTA 408 to be selected from doses cleared by the DSMB in Part 1.
Section 7.2 Number of Patients	Up to ~~52~~ 68 patients will be enrolled in this study.	Allow up to 16 additional patients (2 cohorts of 8 patients)
Section 7.3 Treatment Assignment	Patients enrolled in the first cohort for Part 1 will be randomized 3:1 to receive RTA 408 2.5 mg or placebo. After the Week 2 visit, patients receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg starting on Day 15 unless a DLT is observed. Patients enrolled in the second cohort will be randomized 3:1 to receive RTA 408 10 mg or placebo. Patients enrolled in the third cohort in Part 1 will be randomized 3:1 to receive RTA 408 (at a dosage strength that does not exceed 100% dose escalation from the second cohort) or placebo. Patients enrolled in the fourth cohort in Part 1 will be randomized 3:1 to receive RTA 408 (at a dosage strength that does not exceed 100% dose escalation from the third cohort) or placebo. Patients enrolled in Part 2 of the study will be randomized 1:1:1 to one of 2 dose levels of RTA 408~~2.5 mg, RTA 408 10 mg~~ selected from Part 1, or placebo.	Clarification given changes to study design

Section	Protocol Version 4	Rationale
Section 7.4.1 Selection of Doses	This 2-part study will evaluate the safety, efficacy, and PD of RTA 408 at ~~3~~ several dose levels (2.5 mg, 5 mg, and 10 mg, and two additional dose levels not exceeding 100% dose escalation from the prior dose level) in the treatment of patients with Friedreich's ataxia. ~~Initial safety, pharmacokinetic (PK), and PD data from an ongoing Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors (Study 408-C-1303) suggest that a 2.5-mg doses of RTA 408 is well tolerated and provides pharmacologically relevant systemic exposure to RTA 408. No Grade 2 or higher drug-related adverse events (AEs) or drug-related serious adverse events (SAEs) have been observed to date in Study 408-C-1303. The protocol safety review committee for Study 408-C-1303 elected to dose to 5 mg, , and preliminary safety data from the 5-mg cohort are consistent with the 2.5-mg cohort.~~ . PD data from the 2.5-mg cohort in Study 408-C-1303, an ongoing Phase 1 study of RTA 408 monotherapy in patients with advanced solid tumors, suggest that this may be in or near a pharmacologically active dose range based on an apparent induction of Nrf2 target genes in peripheral blood mononuclear cells after 28 days of treatment. This observation is consistent with the fact that plasma RTA 408 concentrations achieved at the 2.5-mg dose level are above those required for *in vitro* activation of Nrf2. ~~Because the 2.5-mg dose may be near the minimal pharmacologically active dose level~~ Dose escalation up to 100% from the third cohort was selected as the highest potential dose in this study in an effort to adequately dose range ~~because it is 4 times the low dose and is expected~~ and to provide good separation of treatment effects between dose groups.	Clarification given changes to study design

Section	Protocol Version 4	Rationale
Section 7.4.2 Dose-Escalation Scheme	After the last patient in the 10-mg cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information ~~from study Part 1~~ to determine if an additional (third) cohort of RTA 408 up to 100% dose escalation (n=6) or placebo (n=2) may be added. After the last patient in the third cohort completes their Week 2 visit, the DSMB and Sponsor will review available data to determine if an additional (fourth) cohort of RTA 408 up to 100% dose escalation (n=6) or placebo (n=2) may be added. After the last patient in the final cohort of Part 1 completes their week 2 visit, the DSMB and Sponsor will review available safety information to make a decision regarding continuation to study Part 2.	Clarification given changes to study design
Section 7.5 Data Safety Monitoring Board	In addition to the monthly reviews of unblinded study data, the DSMB will participate with the Sponsor in the recommendation to open the 10-mg cohort and up to two additional dosing cohorts for enrollment for Part 1 and opening Part 2 described in Section 7.4.2.	Clarification given changes to study design
[redacted]	[redacted]	[redacted]
Table 3	[w] For patients enrolled in the second ~~cohort~~ and subsequent cohorts of Part 1 of the study, blood samples for PK analysis at Visit 4 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 10 should be collected prior to study drug administration.	Clarification regarding timing for PK collections for Cohort 3 and Cohort 4

Section	Protocol Version 4	Rationale
Section 9.1 Description of Study Drug	Depending on cohort dose level (or doses selected for part 2) patients will ingest either 3 or 4 capsules of study drug (1 from each ~~of 3 separate~~ bottle~~s~~ included in study treatment kit) daily throughout the study; study drug is described in Section 10.1. Treatment kits containing up to 30 mg of RTA 408 will include three bottles, each containing 30 count of either active or placebo capsules. Treatment kits containing greater than 30 mg of RTA 408 will be comprised of four bottles, each containing 30 count of either active of placebo capsules. To maintain the study blind, treatment kits used in part 2 will all include the same number of bottles. ~~In the first cohort of Part 1 of the study, patients randomized to RTA 408 2.5 mg will ingest one 2.5 mg capsule and 2 placebo capsules once daily for 2 weeks; those randomized to placebo will ingest 3 placebo capsules once daily. At 2 weeks, all patients will be evaluated for dose escalation and will receive a new kit of study drug whether or not they are dose escalated. Patients randomized to RTA 408 who are dose escalated after 2 weeks will ingest two 2.5-mg capsules and 1 placebo capsule once daily starting on Day 15 and continuing for the remaining 10 weeks; patients randomized to placebo will continue to ingest 3 placebo capsules once daily. Patients who are not dose escalated will continue on their originally randomized study drug for the remaining 10 weeks.~~ ~~In the second cohort enrolled in Part 1 of the study, patients randomized to RTA 408 10 mg will ingest one 10 mg capsule and 2 placebo capsules once daily for 12 weeks; those randomized to placebo will ingest 3 placebo capsules once daily.~~ ~~In Part 2 of the study, patients randomized to RTA 408 2.5 mg will ingest one 2.5 mg capsule and 2 placebo capsules once daily for 12 weeks. Patients randomized to RTA 408 10 mg will ingest one 10 mg capsule and 2 placebo capsules once daily for 12 weeks. Patients randomized to placebo will ingest 3 placebo capsules once daily.~~ The Sponsor will provide sufficient quantities of study drug to allow for completion of the study.	Kit design modified to allow for higher doses of RTA 408

Section	Protocol Version 4	Rationale
Section 9.2.1 Excluded Medications	• Anti-spasticity agents	Clarification to specify washout period for anti-spasticity agents
Section 9.4 Randomization	The first cohort enrolled in Part 1 will be randomized 3:1 to RTA 408 2.5 mg or placebo. The second cohort enrolled in Part 1 will be randomized 3:1 to RTA 408 10 mg or placebo. Subsequent Part 1 cohorts will be randomized in the same ratio. Patients enrolled in Part 2 will be randomized 1:1:1 to RTA 408 ~~2.5 mg or RTA 408 10 mg or placebo~~ at one of the two selected doses or placebo.	Clarification given changes to study design
Section 9.4 Randomization	Randomization for both Part 1 and Part 2 will be generated ~~dynamically~~ using a centralized IWRS.	Correction. Block randomization will be utilized
Section 9.9.13 Clinical Chemistry	(Table 4) Creatine kinase isozyme (only if creatine kinase is >ULN)	Added
Section 9.9.14 Hematology	As noted in Table 5, HbA1c will only be collected at Screening and Week 12 visits.	Clarification
Section 9.9.14 Hematology	(Table 5) HbA1C (Screening, Week 12)	Clarification
Section 9.9.21 Study Drug Administration	As outlined in section 9.1, ~~The~~ study drug treatment kits will contain either three or four 30-count ~~3~~ bottles of RTA 408 or placebo capsules. ~~and~~ Patients should take 1 capsule from each bottle daily ~~(i.e., a total of 3 capsules daily).~~	Clarification for changes to kit design

Section	Protocol Version 4	Rationale
[redacted]	[redacted]	Clarification
[redacted]	[redacted]	Clarification
Section 10.2 Study Drug Packaging and Labeling	RTA 408 active and placebo capsules ~~All investigational product~~ are contained~~will be packaged~~ in identical primary container closure systems (i.e., 75-cc high-density polyethylene [HDPE] bottles with a foil induction-seal liner and a child-resistant closure). Treatment kits containing either three or four bottles, depending on treatment assignment, will be~~and~~ provided to patients for self-administration. ~~Each kit contains 3 bottles. For both study parts, each kit will contain either (A) 3 bottles of placebo (for those randomized to placebo); (B) 1 bottle of RTA 408 2.5 mg and 2 bottles of placebo (for those randomized to RTA 408 2.5 mg); (C) 2 bottles of RTA 408 2.5 mg and 1 bottle of placebo (for those in Part 1 who dose escalate to RTA 408 5 mg); or (D) 1 bottle of RTA 408 10 mg and 2 bottles of placebo (for those randomized to 10 mg).~~	Kit design modified to allow for higher doses of RTA 408
Section 12.7 Reporting Serious Adverse Events	For other SAEs that do not meet the fatal or life-threatening unexpected criteria but are ~~deemed by the investigator~~reported to be associated with the use of the study drug (that is, "possible" or "probable" in causality assessment), the Sponsor or its designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies.	Clarification

Section	Protocol Version 4	Rationale
Section 13.2.2 Platelet Analysis	Mitochondrial function and biochemical changes in ~~the frataxin levels~~ metabolites of interest will be analyzed from platelet samples.	Clarification
Section 14.3.2 Primary Efficacy Analysis	Peak work from Part 2 for the pooled patients treated with RTA 408 ~~(2.5 mg and 10 mg)~~ will be compared with placebo after 12 weeks of treatment by repeated measures analysis of covariance, with treatment group, time, and the interaction between treatment and time as fixed factors and baseline peak work as a covariate.	Clarification to allow for other potential doses in Part 2



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Section	Protocol Version 3	Rationale
Section 6.3	• To characterize the pharmacokinetics of RTA 408 and potential metabolites after oral administration of RTA 408 Capsules	PK characterization added as an objective of the study, per FDA recommendation
Section 7.1	~~At~~ After the Week 2 visit, each patient will dose escalate starting on Day 15,	Clarification
Section 7.3	After the Week 2 ~~weeks~~ visit, patients receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg starting on Day 15 unless a DLT is observed.	Clarification
Section 7.4.2	The patients receiving RTA 408 2.5 mg will begin receiving RTA 408 5 mg on Day 15 and the patients receiving placebo will remain on placebo in a blinded fashion.	Clarification
Section 7.4.4	Each patient will dose escalate ~~at the Week 2 visit~~ starting on Day 15, unless a DLT is indicated by the investigator.	Clarification
Section 7.7	Table 3 lists the overall schedule of assessments for the study. Schedules of assessments for Part 1 and Part 2 are listed individually in Appendix 1.	Clarification
Table 3	Neurologic FARS ~~(full or modified FARS)~~	Clarification
Table 3	PK analysis added at Visit 7 for Cohort 1 in Part 1 of the study	Additional samples collected for PK analysis purposes
Table 3	~~p~~ Study drug should be administered in the presence of study staff in the clinic on Day 1 after all Day 1 assessments have been completed. Study drug should also be administered in the clinic ~~at~~ on Days 14, 28 (Part 2 only), 56 (Cohort 1, Part 1 only), and ~~28 and Day~~ 84 after the blood collection for predose PK analysis.	Clarification
Table 3	q On study days where multiple assessments are to be completed, the maximal exercise test will be the first functional assessment performed.	Clarification
Table 3	~~r On Day 28 and Day 56, only the modified FARS test should be performed~~	Clarification

Section	Protocol Version 3	Rationale
Table 3	[v] For patients enrolled in the first cohort of Part 1 of the study, blood samples for PK analysis at Visit 4 and Visit 7 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 10 should be collected prior to study drug administration.	Additional samples collected for PK analysis purposes
Table 3	[w] For patients enrolled in the second cohort of Part 1 of the study, blood samples for PK analysis at Visit 4 should be collected prior to study drug administration as well as 1, 2, 4, and 8 hours after study drug administration. A single blood sample for PK analysis at Visit 10 should be collected prior to study drug administration.	Additional samples collected for PK analysis purposes
Table 3	[x] For patients enrolled in Part 2 of the study, blood samples for PK analysis at Visit 5 and Visit 10 should be collected prior to study drug administration.	Clarification
Section 8.2	Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than ~~2~~1.5 times the upper limit of normal of AST, ALT, or creatinine. Levels above this threshold are allowable if attributable to muscle injury	Clarification
Section 8.2	a. Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)	Added moderate or strong inhibitors or inducers of cytochrome P450 3A4 as excluded medications, per FDA recommendation

Section	Protocol Version 3	Rationale
Section 8.2	9. Have a history of clinically significant liver disease (e.g., fibrosis, cirrhosis, hepatitis), or has, at screening, clinically relevant deviations in laboratory tests including any one of the following: a. alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 1.5-fold ULN, b. bilirubin > 1.2-fold ULN, c. alkaline phosphatase (ALP) > 2-fold ULN, d. kidney insufficiency as defined by creatinine level > 1.5 mg/dL, e. albumin < lower limit of normal (LLN)	Exclude patients with clinically significant liver disease, per FDA recommendation
Section 8.3	o Moderate or strong inhibitors or inducers of cytochrome P450 2C8 or 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)	Added moderate or strong inhibitors or inducers of cytochrome P450 3A4 as excluded medications, per FDA recommendation
Section 9.1	Patients randomized to RTA 408 who are dose escalated after 2 weeks will ingest two 2.5-mg capsules and 1 placebo capsule once daily starting on Day 15 and continuing for the remaining 10 weeks;	Clarification
Section 9.2.1	• Moderate or strong inhibitors or inducers of cytochrome P450 3A4 (e.g., carbamazepine, phenytoin, ciprofloxacin, grapefruit juice)	Added moderate or strong inhibitors or inducers of cytochrome P450 3A4 as excluded medications, per FDA recommendation
Section 9.2.2	Patients taking medications with intermittent or as-needed schedules should try to avoid taking the concomitant medication on days when PK samples will be collected (i.e., Visits 4, 5, 7, and 10), as medically feasible.	Clarification

Section	Protocol Version 3	Rationale
Table 4	Creatinine ~~(enzymatic)~~	Clarification
Section 9.9.21	Study drug should be taken with water at the times indicated in Table 3, except on Days 1, 14, 28 (Part 2 only), ~~Day 28~~ 56 (Cohort 1; Part 1 only), and ~~Day~~ 84, when study staff will administer study drug at the clinic following all assessments on Day 1, and after the pre-dose blood sample for PK analysis on Days 14, 28 (Part 2 only), 56 (Cohort 1; Part 1 only), and 84 ~~and following collection of the blood samples for PK analysis on Days 28 and 84~~. The date and time of the 2 most recent doses of study medication prior to Days 14, 28 (Part 2 only), 56 (Cohort 1; Part 1 only)~~28~~, and 84 will be recorded for PK analysis.	Clarification
[redacted]	[redacted]	Clarification
Section 9.9.34	Blood samples for plasma PK analysis will be collected at the times indicated in Table 3. Blood sample collection instructions are detailed in the lab manual. All pre-dose blood samples should be collected within 1 hour prior to dose administration. Blood samples collected in Part 1 of the study after dose administration at Visit 4 and Visit 7 (Cohort 1 only) should be collected ± 15 minutes of the scheduled time.	Clarification
Section 9.9.34	Detailed sample processing instructions will be provided for isolation, storage, and shipment of plasma PK samples.	Clarification
Section 14.2.1	The PK variables include RTA 408 plasma concentration-time data and metabolite concentration-time data (if available), and relevant pharmacokinetic parameter values (e.g., C_{max}, T_{max}, AUC) for each analyte.	Clarification
Appendix 1	Schedule of events for Part 1 and Part 2 added	Clarification
Appendix 3	Eye chart used during low contrast visual acuity testing removed from Appendix 3.	Eye charts will be included in a study manual



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- The list of abbreviations has been updated.

Section	Protocol Version 2	Rationale
Section 2	Up to ~~5~~ 7 study centers in the US	Increased the number of study centers
Section 2	Estimated date last patient completed: ~~December 2015~~ June 2016	Updated estimated timeline based on revised study design
Section 6.1	• To evaluate the change in peak work~~load~~ during maximal exercise testing	Changed to peak work (specified in watts/kg) instead of peak workload (specified in watts) as the primary endpoint
[redacted]	• [redacted]	Clarification

Section	Protocol Version 2	Rationale
Section 7.1	~~Part 1: The first part of this study will be an open-label, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg and 10 mg in patients with Friedreich's ataxia. An initial 3 patients will be enrolled in the study at the 2.5-mg dose level. After these 3 patients complete their Week 4 visit, the data safety monitoring board (DSMB) and Sponsor will review all available safety information and make a recommendation regarding escalation to the 10-mg dose level or enrollment of an additional 3 patients at the 2.5-mg dose level. When the 10-mg dose level is opened, 3 patients will be enrolled. After these 3 patients complete their Week 4 visit, the DSMB and Sponsor will review all available safety information to make a decision regarding continuation to study Part 2 or enrollment of an additional 3 patients at the 10-mg dose level.~~ Part 1: The first part of this study will be a randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg, 5 mg, and 10 mg in patients with Friedreich's ataxia. An initial cohort of 8 patients will be randomized 3:1 to RTA 408 2.5 mg (n=6) or placebo (n=2). At the Week 2 visit, each patient will dose escalate unless a dose-limiting toxicity (DLT) is reported in that patient (Section 7.4.3). Patients originally randomized to RTA 408 2.5 mg will dose escalate to RTA 408 5 mg, and those randomized to placebo will continue on placebo in a blinded fashion. After the last patient in the first cohort completes their Week 4 visit (i.e., 2 weeks on 2.5 mg daily [or matching placebo] followed by 2 weeks on 5 mg daily [or matching placebo]), the data safety monitoring board (DSMB) and Sponsor will review all available safety information and make a decision regarding enrollment of the next cohort. If the 10-mg cohort is opened for enrollment, an additional 8 patients will be randomized 3:1 to RTA 408 10 mg or placebo. After the last patient randomized to RTA 408 10 mg or placebo completes their Week 2 visit, the DSMB and Sponsor will review all available safety information to make a decision regarding continuation to Part 2 of the study. Review of data for safety, dose escalation, and continuation to Part 2 are guided by the dose-escalation scheme in Section 7.4.2. All patients in Part 1 will continue taking study drug for a total of 12 weeks.	Revised design for Part 1 of the study based on FDA feedback
Section 7.1	Assuming that ~~both~~ the 2.5-mg, 5-mg and 10-mg doses have been deemed acceptable in Part 1	Addition of 5-mg dose level in Part 1
Section 7.1	~~Randomization~~ Patients will be stratified by peak work~~load~~ at baseline (>~~90~~ 0.8 watts [W]/kg vs. ≤~~90~~0.8 W/kg).	Clarification

Section	Protocol Version 2	Rationale
Section 7.1	All qualified patients enrolled in the study (i.e., both Part 1 and Part 2) will follow ~~the same~~ nearly identical schedules of assessments...	Clarification
Section 7.2	Up to ~~48~~ 52 patients will be enrolled in this study.	Increased study size due to change in design for Part 1
Section 7.3	~~Patients enrolled in Part 1 of the study will be assigned RTA 408 at the current enrolling dose level (2.5 mg or 10 mg). Patients enrolled in Part 2 of the study will be randomized 1:1:1 to RTA 408 2.5 mg, RTA 408 10 mg, or placebo using an Interactive Web Response System (IWRS). Randomization will be stratified by peak workload at baseline (>90 W vs. ≤90 W).~~ Patients enrolled in the first cohort for Part 1 will be randomized 3:1 to receive RTA 408 2.5 mg or placebo. After 2 weeks, patients receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg unless a DLT is observed. Patients enrolled in the second cohort will be randomized 3:1 to receive RTA 408 10 mg or placebo. Patients enrolled in Part 2 of the study will be randomized 1:1:1 to RTA 408 2.5 mg, RTA 408 10 mg, or placebo. All randomizations will be performed using an Interactive Web Response System (IWRS). Patients enrolled in Part 2 will be stratified by peak work at baseline (>0.8 W/kg vs. ≤0.8 W/kg).	Clarification of treatment assignment and dose escalation in Part 1
Section 7.4.1	This 2-part study will evaluate the safety, efficacy, and PD of RTA 408 at ~~2~~3 dose levels (2.5 mg, 5 mg, and 10 mg) in the treatment of patients with Friedreich's ataxia.	Addition of 5-mg dose level in Part 1

Section	Protocol Version 2	Rationale
Section 7.4.2	~~The open-label, dose-escalation portion of the study (Part 1) will first evaluate the safety of RTA 408 at 2.5 mg to make a decision regarding escalation to 10 mg, and then evaluate the safety of RTA 408 at 10 mg to make a decision regarding enrollment of the randomized, double-blind, placebo-controlled portion of the study (Part 2).~~ ~~Three patients will be enrolled at each dose level in Part 1. After the first 3 patients have completed the Week 4 visit, an overall review of safety information for all enrolled patients will be conducted by the DSMB and Sponsor. Additionally, the following rules for dose escalation and enrollment of Part 2 will be applied based on assessment of dose-limiting toxicities (DLTs) through Week 4 for patients enrolled at the current dose level under evaluation:~~ ~~1. If no patient (0/3) experiences a DLT, then dose escalation (or enrollment of Part 2) may occur.~~ ~~2. If 1 patient (1/3) experiences a DLT, then 3 additional patients will be enrolled at the same dose level and the following rules will be applied:~~ ~~a. If none of the additional patients (0/3) experiences a DLT (i.e., 5/6 patients did NOT experience a DLT at the current dose level), then dose escalation (or enrollment of Part 2) may occur.~~ ~~b. If 1 or more additional patient (≥ 1/3) experiences a DLT (i.e., ≥2/6 patients experience a DLT at the current dose level), then no further patients will be enrolled in the cohort and the maximum tolerated dose (MTD) will be considered to have been exceeded. Dose escalation will not occur.~~ ~~3. If ≥2 patients (≥2/3) experience a DLT, then no further patients will be enrolled in the cohort and the MTD will be considered to have been exceeded. Dose escalation will not occur.~~	Based on FDA feedback, 3+3 design changed to enroll 6 patients on active treatment in each cohort of Part 1

Section	Protocol Version 2	Rationale
Section 7.4.2	In Part 1 of the study, an initial cohort of 8 patients will be randomized 3:1 to RTA 408 2.5 mg (n=6) or placebo (n=2). Each patient in the first cohort will be evaluated for intrapatient dose-escalation by their investigator at the Week 2 visit. If no DLTs are observed by Week 2 for that patient, the patient will dose escalate. The patients receiving RTA 408 2.5 mg will begin receiving RTA 408 5 mg and the patients receiving placebo will remain on placebo in a blinded fashion. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. Patients who are deemed inappropriate for dose escalation will continue on their originally randomized dose (i.e., 2.5 mg or placebo) throughout the remainder of the study. After the last patient in the initial cohort completes their Week 4 visit, the DSMB and Sponsor will review all available safety information from this cohort and make a recommendation regarding opening the next cohort to be randomized 3:1 to RTA 408 10 mg (n=6) or placebo (n=2). After the last patient in the 10-mg cohort completes their Week 2 visit, the DSMB and Sponsor will review all available safety information from study Part 1 to make a decision regarding continuation to study Part 2.	Clarified process for dose escalation, including addition of intra-patient dose escalation for Cohort 1

Section	Protocol Version 2	Rationale
Section 7.4.3	~~Because any potential RTA 408 DLTs are expected to occur relatively soon after treatment initiation based on results with a similar Reata compound (de Zeeuw, 2013) the DLT observation period will last through Week 4. Furthermore, during the overall review of safety performed in parallel with the dose-escalation review, the DSMB and Sponsor will also consider safety data obtained from prior cohorts treated at lower doses to determine if latent AEs occur outside of the 4-week DLT window. The Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) will be used to grade intensity of AEs that may be considered a DLT, except where related to transaminase laboratory values. Nrf2 activation by RTA 408 and related analogs has been shown to upregulate the production of transaminases. The transaminase upregulation is a pharmacologic and transcriptional response and has not been shown to be associated with liver toxicity in animal studies or clinical studies with a related analog (Hong, 2012; Pergola, 2011). Therefore, the criteria for a DLT related to transaminase laboratory values will be defined using the United States (US) Food and Drug Administration (FDA) Guidance for Industry on drug-induced liver injury (US FDA, 2009) rather than using CTCAE.~~ ~~The determination of DLT will be defined in each patient as all toxicity Grade ≥3 (using CTCAE, version 4.03), except as noted below:~~ ~~• Nausea and vomiting will be considered a DLT if Grade 3 toxicity persists after optimal medical therapy~~ ~~• Any hepatobiliary disorders of Grade ≥2 (from CTCAE, version 4.03, pages 24-25) will be considered a DLT. Note that laboratory measurements are included in a separate section of the CTCAE~~ ~~• Changes in ALT, AST, and total bilirubin levels must meet 1 of the following criteria to be considered a DLT:~~ ~~o ALT or AST >8X upper limit of normal (ULN)~~ ~~o ALT or AST >5X ULN for more than 2 weeks~~ ~~o ALT or AST >3X ULN and (total bilirubin >2X ULN or international normalized ratio >1.5)~~ ~~o ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)~~	Based on FDA feedback, removed pre-specified dose-limiting toxicity criteria

Section	Protocol Version 2	Rationale
Section 7.4.3	The assessment of a DLT (i.e., a side effect serious enough to prevent an increase in dose) will be based on the clinical judgment of the investigator. Suspected DLTs should be discussed with the medical monitor. If an investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor.	Clarification that dose-limiting toxicity will be based on the clinical judgment of the investigator
Section 7.4.4	~~Intrapatient dose escalation or dose adjustment will not be allowed. Patients will self-administer study treatment orally once daily at the assigned (or randomized) dose level until they have completed 12 weeks (84 days) of study treatment, discontinued from study treatment, or withdrawn consent.~~ Intra-patient dose escalation will only occur for the first cohort of 8 patients randomized in Part 1 of the study (i.e., those patients randomized to RTA 408 2.5 mg or placebo). Investigators, and not the DSMB, will make intra-patient dose-escalation decisions during the first cohort of Part 1. Each patient will dose escalate at the Week 2 visit, unless a DLT is indicated by the investigator. Patients originally randomized to RTA 408 2.5 mg will dose escalate to RTA 408 5 mg, and those randomized to placebo will remain on placebo in a blinded fashion. If the investigator cannot come to a firm decision whether or not to dose escalate a patient, he or she should discuss the relevant safety information with the medical monitor. If the investigator determines the patient should not be dose escalated, that patient should continue on their originally randomized dose (i.e., 2.5 mg or placebo) throughout the remainder of the study visits. No other patients are eligible for intra-patient dose escalation.	Added intrapatient dose escalation criteria for patients enrolled in Part 1 of the study
Section 7.5	~~Since Part 1 of the study is open label, there will only be open sessions of the DSMB's meetings during Part 1. During Part 2 of the study, blinded Sponsor representatives and the study's blinded statistical group may be present at the open sessions of the DSMB's meetings; however, they will not have access to any unblinded data.~~	Removed text because Part 1 and Part 2 will be blinded
Section 7.5	In addition to the monthly reviews of unblinded study data, the DSMB will participate with the Sponsor in ~~dose escalation recommendations~~ the recommendation to open the 10-mg cohort for enrollment for Part 1 and opening Part 2 described in Section 7.4.2. However, investigators, and not the DSMB, will make intra-patient dose-escalation decisions during the first cohort of Part 1.	Clarification

Section	Protocol Version 2	Rationale
Table 3	BNP and NT-proBNP collection added to schedule of assessments	BNP and NT-proBNP collected separately from clinical chemistry samples
Table 3	Electrocardiogram: added at Visit 4 Study drug return and pill count: added at Visit 4 Study drug administration: added at Visit 4	Added safety assessment and modified study drug logistics at the Week 2 visit (Visit 4)
Table 3	[e] Assessments for Visit 4 must be collected at the study center if patients are enrolled in Part 1 of the study. If patients are enrolled in Part 2 of the study, Visit 4 assessments may be collected by a home health nurse	Week 2 study center visit required in Part 1 for dose escalation decision; not needed in Part 2
Table 3	[h] At Week 2, electrocardiogram is only required for patients in Part 1 of the study.	Week 2 ECG needed for dose escalation decision in Part 1; not needed in Part 2.
Table 3	[j] Patients must be allowed to rest for a minimum period of 1 hour following maximal exercise test before this blood sample is collected (at the same time as all central lab blood draws). This sample should be taken with the patient in the same position (e.g., sitting or semi-recumbent) at all appropriate visits.	Added delay between BNP collection and maximal exercise testing because exercise can affect BNP levels
Table 3	[m] At Week 2, study drug dispensation is only required for patients in the first cohort of Part 1 of the study.	Clarification
Table 3	[o] At Week 2, study drug return, pill count, and diary check are only required for patients in the first cohort of Part 1 of the study.	Clarification
Table 3	[r] On Day 28 and Day 56, only the modified FARS test should be performed.	Clarification
Table 3	[v] Platelet collection will only be conducted at Sponsor-qualified sites.	Clarification

Section	Protocol Version 2	Rationale
Section 8.1	~~7. Have a peak workload during maximal exercise testing of 55 W to 125 W 0≤ 1.5 W/kg~~	Removed peak work elgibility criteria
Section 8.2	3. Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia, including but not limited to any of the following: e. History of hospitalization for heart failure in the last five years	Clarification
Section 8.2	5. Have known or suspected active drug or alcohol abuse, as per investigator judgment	Clarification
Section 8.2	6. Have clinically significant abnormalities of clinical hematology or biochemistry, including but not limited to elevations greater than ~~1.5~~2 times the ~~ULN~~upper limit of normal of AST, ALT, or creatinine. Levels above this threshold are allowable if attributable to muscle injury	Clarification
Section 8.2	17. Have had significant suicidal ideation within 1 month prior to Screening Visit as per investigator judgment or any history of suicide attempts	Clarification
Section 8.3	Patients may repeat the screening procedures once to qualify for the study ~~with approval from the medical~~ monitor if they have:	Clarification
Section 8.3	• An abnormal laboratory test value that may normalize, in the opinion of the investigator (rescreening may be performed once test value is within normal range ~~or grade <2 CTCAE)~~	Clarification
Section 8.3	• Failed screening because of operational challenges (rescreening may be performed no fewer than 2 weeks from the date of screen failure)	Clarification

Section	Protocol Version 2	Rationale
Section 9.1	~~In Part 1 of the study, patients will ingest 1 capsule daily for 12 weeks. In Part 2 of the study, patients will ingest 2 capsules daily for 12 weeks. Each capsule will contain either RTA 408 drug product, 2.5 mg or 10 mg, or placebo as described in Section 10.1. Reata Pharmaceuticals…~~ All patients will ingest 3 capsules of study drug (1 from each of 3 separate bottles) daily throughout the study, which is described in Section 10.1. In the first cohort of Part 1 of the study, patients randomized to RTA 408 2.5 mg will ingest one 2.5-mg capsule and 2 placebo capsules once daily for 2 weeks; those randomized to placebo will ingest 3 placebo capsules once daily. At 2 weeks, all patients will be evaluated for dose-escalation and will receive a new kit of study drug whether or not they are dose-escalated. Patients randomized to RTA 408 who are dose escalated after 2 weeks will ingest two 2.5-mg capsules and 1 placebo capsule once daily for the remaining 10 weeks; patients randomized to placebo will continue to ingest 3 placebo capsules once daily. Patients who are not dose escalated will continue on their originally randomized study drug for the remaining 10 weeks. In the second cohort enrolled in Part 1 of the study, patients randomized to RTA 408 10 mg will ingest one 10-mg capsule and 2 placebo capsules once daily for 12 weeks; those randomized to placebo will ingest 3 placebo capsules once daily. In Part 2 of the study, patients randomized to RTA 408 2.5 mg will ingest one 2.5-mg capsule and 2 placebo capsules once daily for 12 weeks. Patients randomized to RTA 408 10 mg will ingest one 10-mg capsule and 2 placebo capsules once daily for 12 weeks. Patients randomized to placebo will ingest 3 placebo capsules once daily.	Additional details added surrounding study drug administration in Part 1 and Part 2
Section 9.2.1	• Anticoagulant therapy, with the exception of a daily baby aspirin (up to 81 mg)	Clarification
Section 9.2.1	~~Use of these prohibited medications during the study should be documented as a protocol deviation, but patients should continue in the study:~~ ~~• Any other investigational drug~~	Clarification

Section	Protocol Version 2	Rationale
Section 9.3	~~Beginning with the Week 4 Visit (Visit 5), patients will return all unused pills every 4 weeks (Visits 7 and 10) and will be dispensed a new kit of study drug.~~ All patients will return all bottles and unused pills at the Weeks 4, 8, and 12 visits and will be dispensed a new kit of study drug at the Weeks 4 and 8 visits. In addition, patients in the first cohort of Part 1 will return all unused pills at the Week 2 visit and will be dispensed a new kit of study drug at that time.	Modified study drug dispensation and collection for Part 1 of the study
Section 9.4	~~Patients enrolled in Part 1 of the study will be assigned to RTA 408 Capsules (2.5 mg or 10 mg) as determined by the dose-escalation scheme. Patients enrolled in Part 2 will be randomly assigned to RTA 408 2.5 mg or RTA 408 10 mg or placebo using a 1:1:1 assignment ratio using a centralized IWRS. Randomization will be generated dynamically within the IWRS and will be stratified by peak workload at baseline (>90 W vs. ≤90 W).~~ The first cohort enrolled in Part 1 will be randomized 3:1 to RTA 408 2.5 mg or placebo. The second cohort enrolled in Part 1 will be randomized 3:1 to RTA 408 10 mg or placebo. Patients enrolled in Part 2 will be randomized 1:1:1 to RTA 408 2.5 mg or RTA 408 10 mg or placebo. Randomization for both Part 1 and Part 2 will be generated dynamically using a centralized IWRS. Randomization for Part 2 will be stratified by peak work at baseline (> 0.8 W/kg vs. ≤ 0.8 W/kg).	Modified randomization in Part 1 to be 3:1 RTA 408 vs. placebo. Stratification criteria specified in watts/kg.
Section 9.5	~~Part 1 will be open label.~~ Some Sponsor personnel may have access to treatment assignments during dose escalation (Part 1), but during Part 2, all Sponsor personnel will be blinded to treatment assignment.	Clarification
Section 9.7.1	Women of childbearing potential (WOCBP) are female patients who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation or chemotherapy, and are not postmenopausal for at least 1 year.	Clarification
Section 9.7.2	• Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.) The vasectomized partner should be the sole partner for that subject.	Clarification

Section	Protocol Version 2	Rationale
Section 9.9	All assessments occur in the study center clinic, with the exception of those assessments for Visits 3 (all patients) and 4~~,~~ (patients in Part 2 only), which may be performed by a home health visit nurse (at appropriate locations and approved by Sponsor), and ~~the~~ those assessments for Visits 7 and 9, which will be performed via telephone contact~~ visits (Visits 7 and 9)~~.	Clarification
Section 9.9.7	However, patients with mild to moderate cardiomyopathy associated with Friedreich's ataxia are not excluded.	Clarification
Section 9.9.16	Blood samples will be collected for N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and BNP at the times indicated in Table 3 (at the same time as the central lab blood collection). Since NT-proBNP may be affected by recent exercise, patients must be allowed to rest for a minimum period of 1 hour following study-specific exercise testing prior to obtaining this blood sample. This sample should be taken with the patient in the same position at all appropriate visits (e.g., sitting or semi-recumbent).	Clarification that blood collection for BNP and NT-proBNP is separate from the blood collection for clinical chemistry
Section 9.9.21	The study drug kit will contain 3 bottles, and patients should take 1 capsule from each bottle daily (i.e., a total of 3 capsules daily). ~~In Part 1, the study drug kit contains 1 bottle. Patients should take 1 capsule from the bottle daily. In Part 2, the study drug kit contains 2 bottles. Patients should take 1 capsule from each bottle daily.~~	Clarification that patients should take 1 capsule from each bottle daily
Section 9.9.22	~~Patients~~Sites should complete a telephone visit contact with the patient to assess AEs and concomitant medications at the times indicated in Table 3. Sites should make at least 3 attempts to contact the patient within the visit window if contact attempts are unsuccessful.	Clarification
Section 9.9.25	Instructions will be provided in the study manual. The FARS examination should be completed by one of the neurologists at the site delegated to complete this assessment.	Clarification
Section 9.9.28	Instructions ~~are~~ will be provided in the study manual~~Appendix 3~~.	Clarification

Section	Protocol Version 2	Rationale
[redacted]	[redacted]	Clarification
Section 9.9.34	Blood samples will be collected at the times indicated in Table 3. ~~Blood samples (4 mL each) will be collected within spray-dried dipotassium ethylenediaminetetraacetic acid (K2EDTA)-containing Vacutainer® tubes. After collection, blood tubes will be inverted/gently mixed (by hand) 8 to 10 times and then placed on ice. Blood samples will be centrifuged (1,100 – 1,300 G for 10 minutes at 4°C) within 60 minutes after collection. After centrifugation, approximately 1.5 mL of plasma should be transferred into one 2 mL Greiner polypropylene cryogenic tubes that contain approximately 3.75 mg of sodium sulfite (Na2SO3). Samples should be mixed well and the Na2SO3-treated plasma samples should be frozen within 120 minutes after collection. The treated plasma collection samples should be maintained at -20°C or colder until analysis.~~ Blood sample collection instructions are detailed in the lab manual.	Removed details that will be provided separate from the protocol
Section 9.9.35	Platelet collection will be required only at Sponsor-qualified sites. Procedures for platelet isolation and analysis will be provided in ~~Appendix 8~~ a study manual.	Clarification
Section 9.9.36	Patients at approved sites will have the option of having a home health visit at the Screening Visit and Visit 3~~, and Visit 4~~. If patients are enrolled in Part 2 of the study, Visit 4 assessments may be collected by a home health nurse. Once the patient has been enrolled in the study, the patient has the option of having a home health visit at Visit 3 and Visit 4 (for patients enrolled in Part 2 only) to complete the required lab collection….	Clarified that Visit 4 can be conducted by a home health nurse only for patients enrolled under Part 2 of the study

Section	Protocol Version 2	Rationale
Section 10.2	~~For Part 1, each kit contains 1 bottle of either RTA 408 2.5 mg or 10 mg capsules. For Part 2, each kit contains 2 bottles, 1 bottle of placebo and 1bottle of either placebo, RTA 408 2.5 mg, or RTA 408 10 mg capsules.~~ Each kit contains 3 bottles. For both study parts, each kit will contain either (A) 3 bottles of placebo (for those randomized to placebo); (B) 1 bottle of RTA 408 2.5 mg and 2 bottles of placebo (for those randomized to RTA 408 2.5 mg); (C) 2 bottles of RTA 408 2.5 mg and 1 bottle of placebo (for those in Part 1 who dose escalate to RTA 408 5 mg); or (D) 1 bottle of RTA 408 10 mg and 2 bottles of placebo (for those randomized to 10 mg).	Specified change in study kit design
Section 11.1	The changes in ~~maximal~~ peak work~~load~~…	Clarification
Section 11.8	These parameters include but are not limited to T1 mapping, left ventricular mass, left ventricular mass index, end diastolic volume, and end systolic volume ~~and presence of infarcted myocardial tissue~~.	Clarification
Section 14.1	~~The sample size for Part 1 is based on a traditional 3+3 design for dose escalation with up to 6 patients in each cohort. With 24 patients enrolled in Part 2 (8 patients per treatment cohort), this study has approximately 80% power to detect an improvement of 22 W in the maximal workload of pooled RTA 408 (n=16) versus placebo (n=8) assuming a two-sided Type I error rate of 0.05, a common standard deviation (SD) within a group of 20 W, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group. The analysis will use repeated measures methodology.~~ The sample size for Part 1 is based on a dose-escalation scheme to evaluate initial safety of RTA 408 in this patient population. With 24 patients enrolled in Part 2 (8 patients per treatment cohort), this study has approximately 80% power to detect an improvement of 0.28 W/kg in the peak work of pooled RTA 408 (n=16) versus placebo (n=8) assuming a two-sided Type I error rate of 0.05, a common within-group standard deviation (SD) of 0.28 W/kg, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group. The analysis will use repeated measures methodology, assuming compound symmetry for the within-subject covariance structure (ρ=0.20).	Changed sample size calculations based on the change in peak work (specified in watts/kg) instead of the change in peak workload (specified in watts)

Section	Protocol Version 2	Rationale
Section 14.1.1	A sample size recalculation in Part 2 will be performed after all 24 patients have been randomized in Part 2 to evaluate the pooled distribution of baseline peak work~~load. If the SD for pooled, baseline peak workload is greater than 20 W, then an additional 12 patients may be enrolled for Part 2. With 36 patients enrolled in Part 2 (i.e., 12 patients per randomized treatment cohort), the 80% power is retained to detect the same difference of 22 W if the SD is up to 25 W, under the same assumptions of a two-sided Type I error rate of 0.05, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group.~~ If the SD for pooled, baseline peak work is greater than 0.28 W/kg or the distribution is not approximately normal, then an additional 12 patients will be enrolled in Part 2. With 36 patients enrolled in Part 2 (i.e., 12 patients per randomized treatment cohort), the 80% power is retained to detect the same difference of 0.28 W/kg if the SD is up to 0.35 W/kg, under the same assumptions of a two-sided Type I error rate of 0.05, and a drop-out rate of no more than 1 in the placebo group and no more than 2 in the pooled RTA 408 group, assuming compound symmetry for the within-subject covariance structure (ρ=0.20).	Changed rules for sample size recalculation based on the variance in peak work (specified in watts/kg) instead of the variance peak workload (specified in watts)
Section 14.2.3	Efficacy variables are ~~maximal workload~~ peak work during maximal exercise testing...	Clarification
Section 14.2.4	The safety variables include results of echocardiogram, ECGs, weight and BMI...	Clarification
Appendix 1	Friedreich's Ataxia Rating Scale instructions removed	Instructions to be provided in a study manual
Appendix 2	Low-contrast visual acuity instructions removed	Instructions to be provided in a study manual