Rationale and Design of a Clinical Study of RTA 408 in Patients with Friedreich's Ataxia

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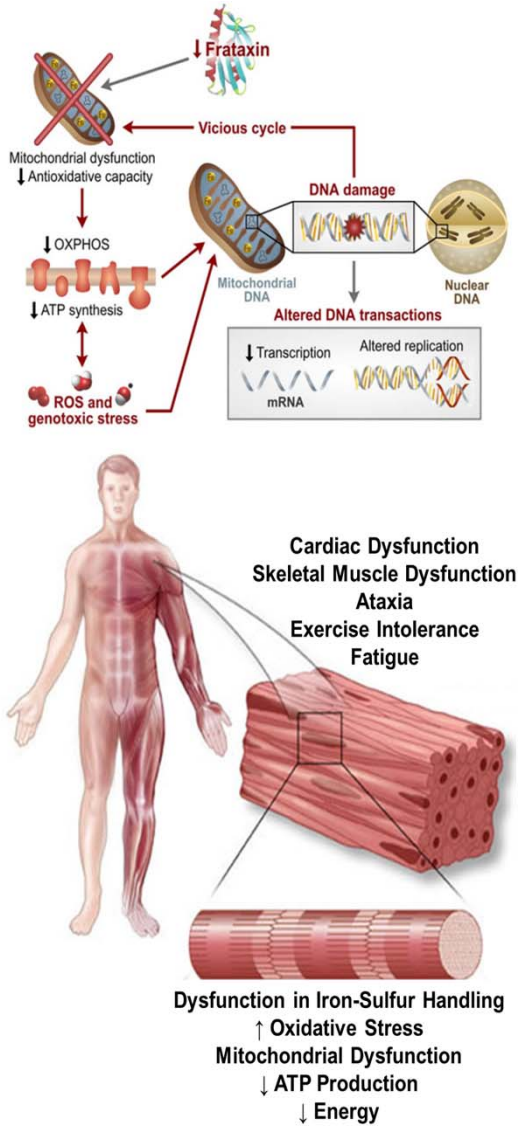
Friedreich's Ataxia

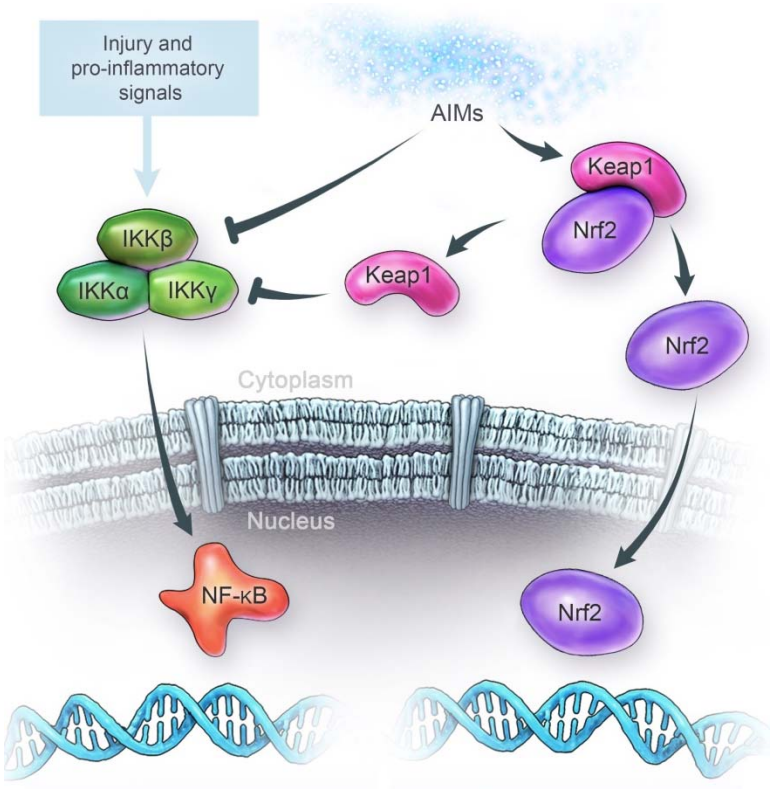
- FA is a genetic disorder caused by a mutation in frataxin, an iron chaperone
- Frataxin mutation leads to:
  - Dysfunctional iron handling
  - Impairment of antioxidative defense mechanisms
  - Generation of excessive Reactive Oxygen Species (ROS)
  - Mitochondrial dysfunction/decreased energy production
  - Epigenetic silencing of frataxin
  - Dysregulation of Nrf2 signaling
- Clinical manifestations include:
  - Ataxia
  - Chronic fatigue and reduced exercise capacity
  - Heart disease, vision loss, and diabetes
  - Reduced quality of life
- No approved drugs

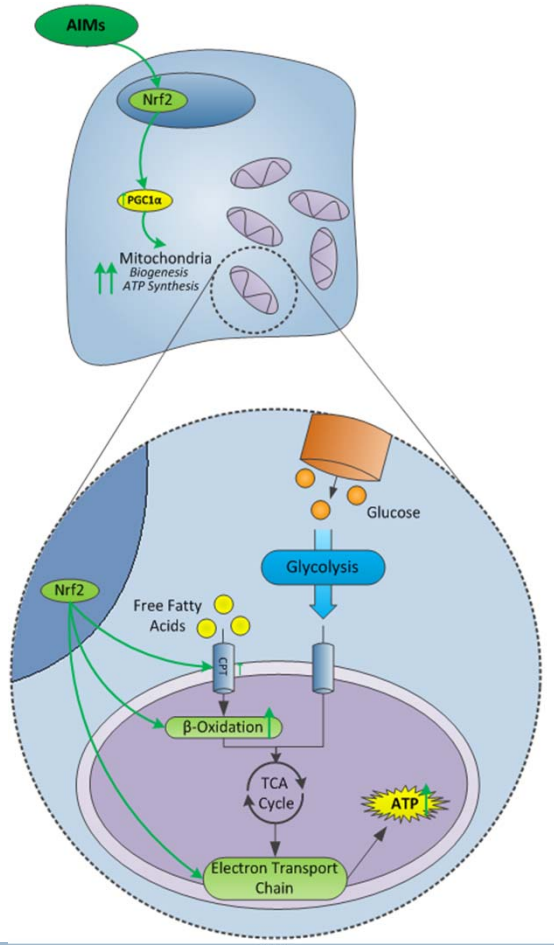


Weidemann F et al., Circulation (2012), Haugen et al., PLoS Genetics (2010); D'Oria V et al., Int J Mol Sci (2013)

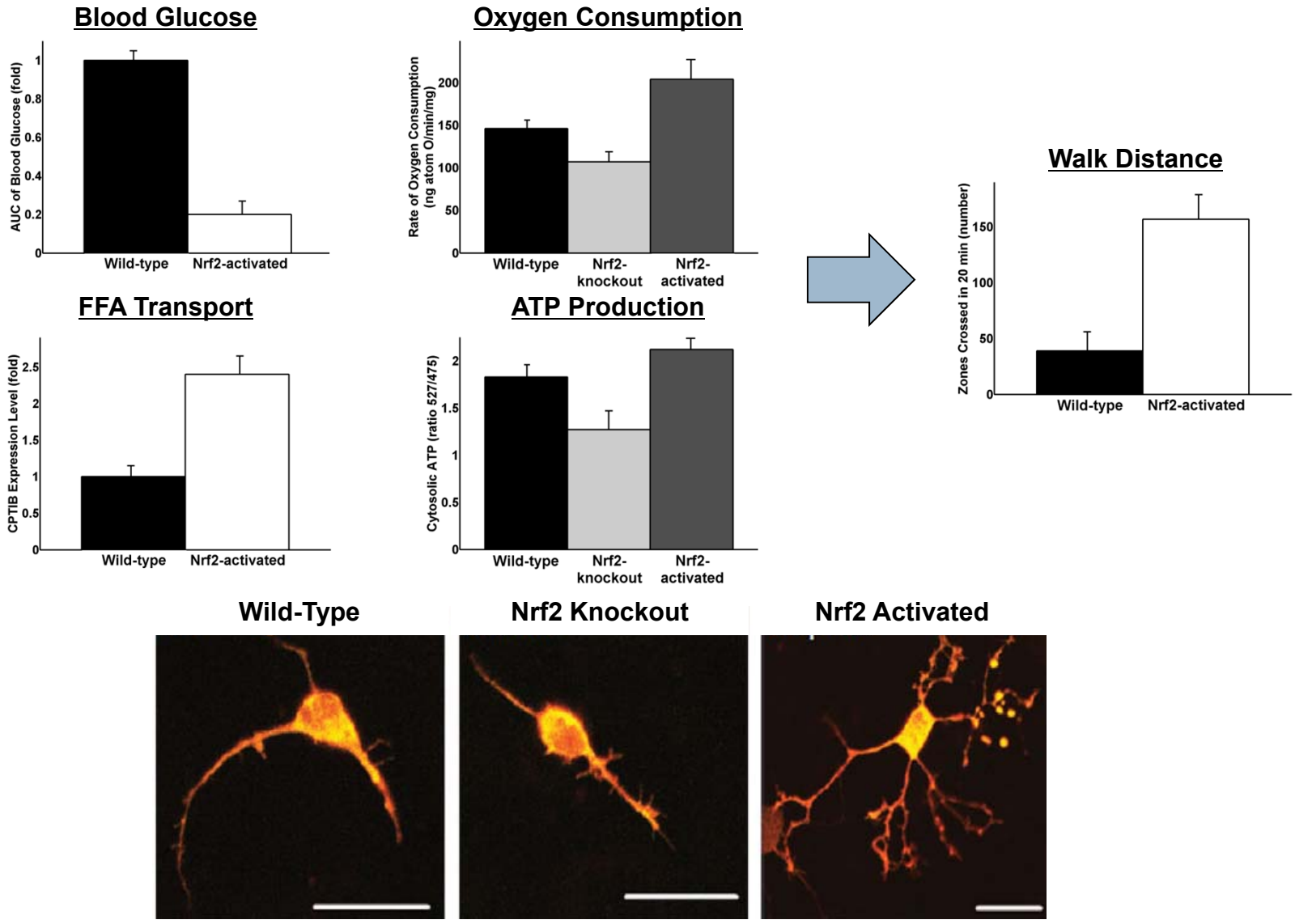
Nrf2 Induction Activates Cell's Antioxidant and Detoxification Pathways and Suppresses NF-κB

- RTA 408 and analogs (AIMs) bind to Keap-1, activating Nrf2 and inhibiting NF-kB
  - Nrf2 induction increases 250+ antioxidant and detoxification enzymes and promotes ATP synthesis
  - NF-kB suppression reduces pro-inflammatory mediators





Genetic Studies Validate Nrf2 as Mitochondrial Target that Improves Exercise Capacity

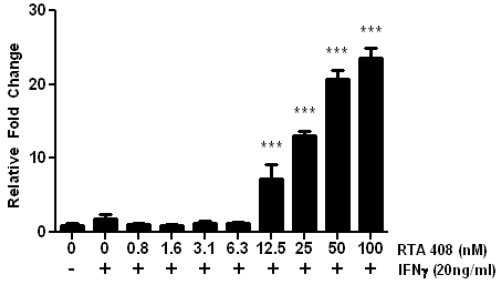


Holstrom et al., Bio Open (2013); Uruno et al., MCB (2013); Ludtmann et al., Biochem J (2014)

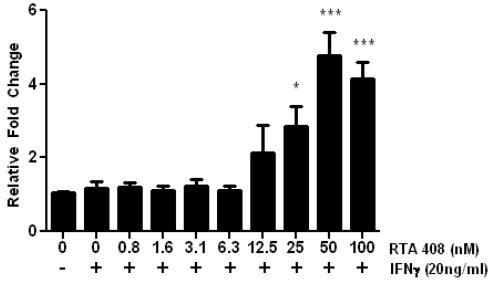
RTA 408 Induces Nrf2 and Suppresses NF-κB at Low Nanomolar Concentration

Nrf2 Target Genes

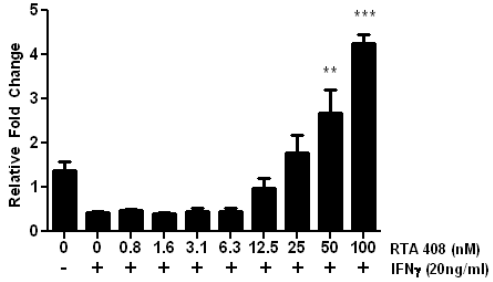
NAD(P)H dehydrogenase, quinone 1 (*Nqo1*)



Thioredoxin reductase 1 (*Txnrd1*)

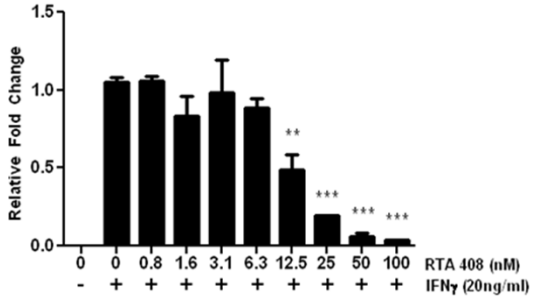


Glutamate-cysteine ligase, catalytic subunit (*Gclc*)

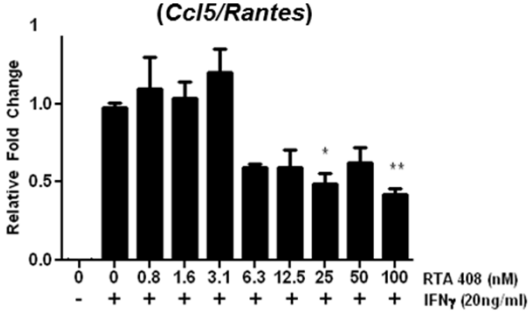


NF-κB Target Genes

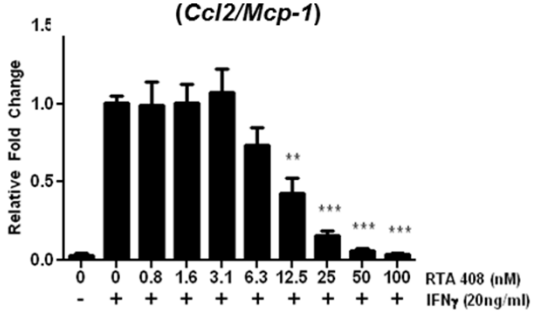
Nitric oxide synthase, inducible (*Nos2*)

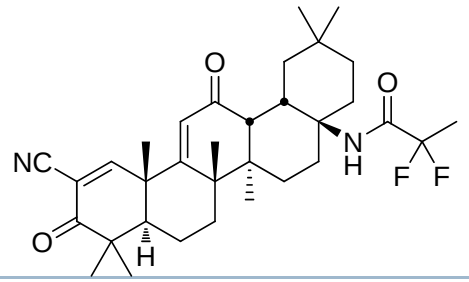


Chemokine (C-C motif) ligand 5 (*Ccl5/Rantes*)



Chemokine (C-C motif) ligand 2 (*Ccl2/Mcp-1*)

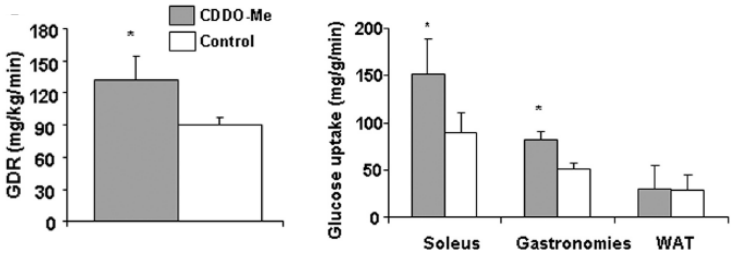




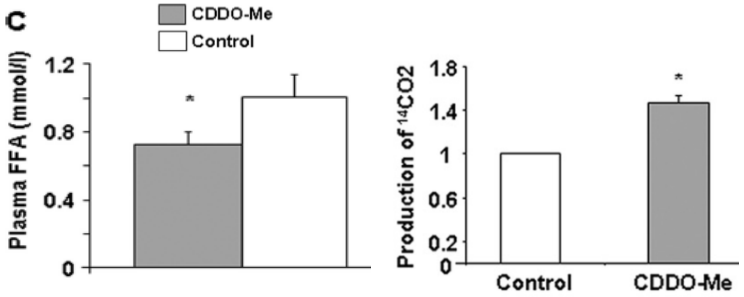
RTA 408 and Analog Improve Energy Production in Preclinical Models

- RTA 408 analog bardoxolone methyl (also known as CDDO-Me) has been shown to improve glucose uptake, fatty acid oxidation, oxygen consumption and ATP levels
- Recent data demonstrate that RTA 408 improves mitochondrial function

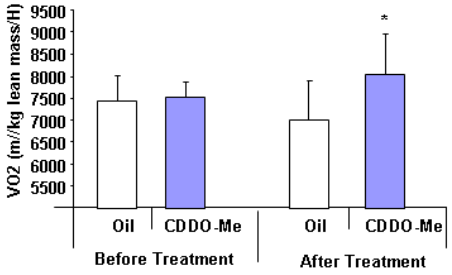
BARD Increases Glucose Uptake



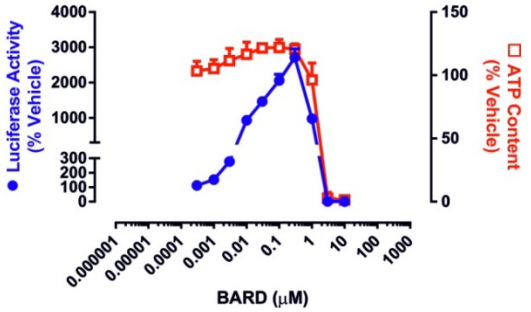
BARD Increases Fatty Acid Uptake and TCA Flux



BARD Increases Oxygen Consumption



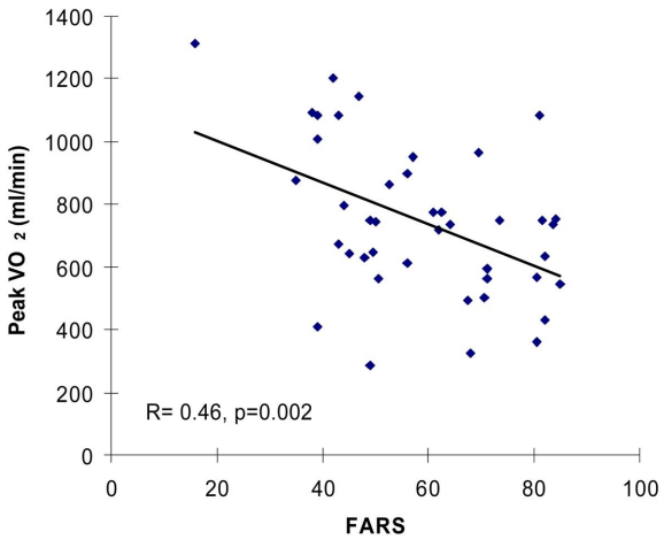
BARD Increases ATP Levels

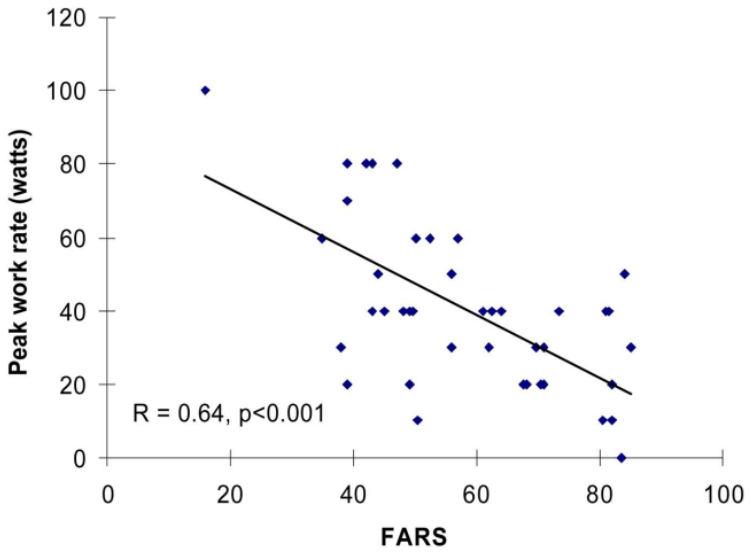


Shin et al., Eur J Pharm (2009); Saha et al., JBC (2010)

Bioenergetic Deficits are Key Features of FA

- Nrf2 signaling is grossly impaired in FA and contributes to oxidative stress, mitochondrial dysfunction and reduced ATP production
  - Reduced nuclear expression of Nrf2
  - Reduced levels of glutathione and antioxidant Nrf2 target genes
- In FA patients, oxygen consumption and exercise capacity are inversely correlated with FARS disease rating scale and length of frataxin mutation
- Peak VO2 and work rate are determined during exercise testing on a recumbent bicycle





Shan Y et al., Antioxidant Redox Signal (2013); D'Oria V et al., Int J Mol Sci (2013); V Paupe et al, PLoS One (2009); Drinkard BE et al., Arch Phys Med Rehabil (2010)

Overview of Design and Objectives of NDA-Enabling FA Study

MOXIe
a study in Friedreich's ataxia

Name	MOXIe: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia
Design	Randomized, placebo-controlled, double-blind, dose-ranging study
Size	40 to 52 patients
Objectives	Primary: • Peak work during maximal exercise testing • Safety and tolerability of RTA 408 Secondary: • Modified Friedreich's ataxia rating scale (FARS) score Exploratory: • SF-36 Health Survey Update score • Fatigue Severity Scale score • 9-hole peg test • Timed 25-foot walk test • Low-contrast letter visual acuity test • Peak oxygen utilization during maximal exercise testing • Pharmacodynamic markers of activity in platelet, cheek swab, and muscle samples

Major Eligibility Criteria

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Major Inclusion Criteria	• Have genetically confirmed Friedreich's ataxia • Have a modified FARS score ≥10 and ≤80 • Be male or female and ≥16 years of age and ≤40 years of age • Have the ability to complete maximal exercise testing • Have a left ventricular ejection fraction ≥40%
Major Exclusion Criteria	• Have uncontrolled diabetes (HbA1c >11.0%) • Have B-type natriuretic peptide (BNP) level >200 pg/mL • 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

Schema for Two-Part Study

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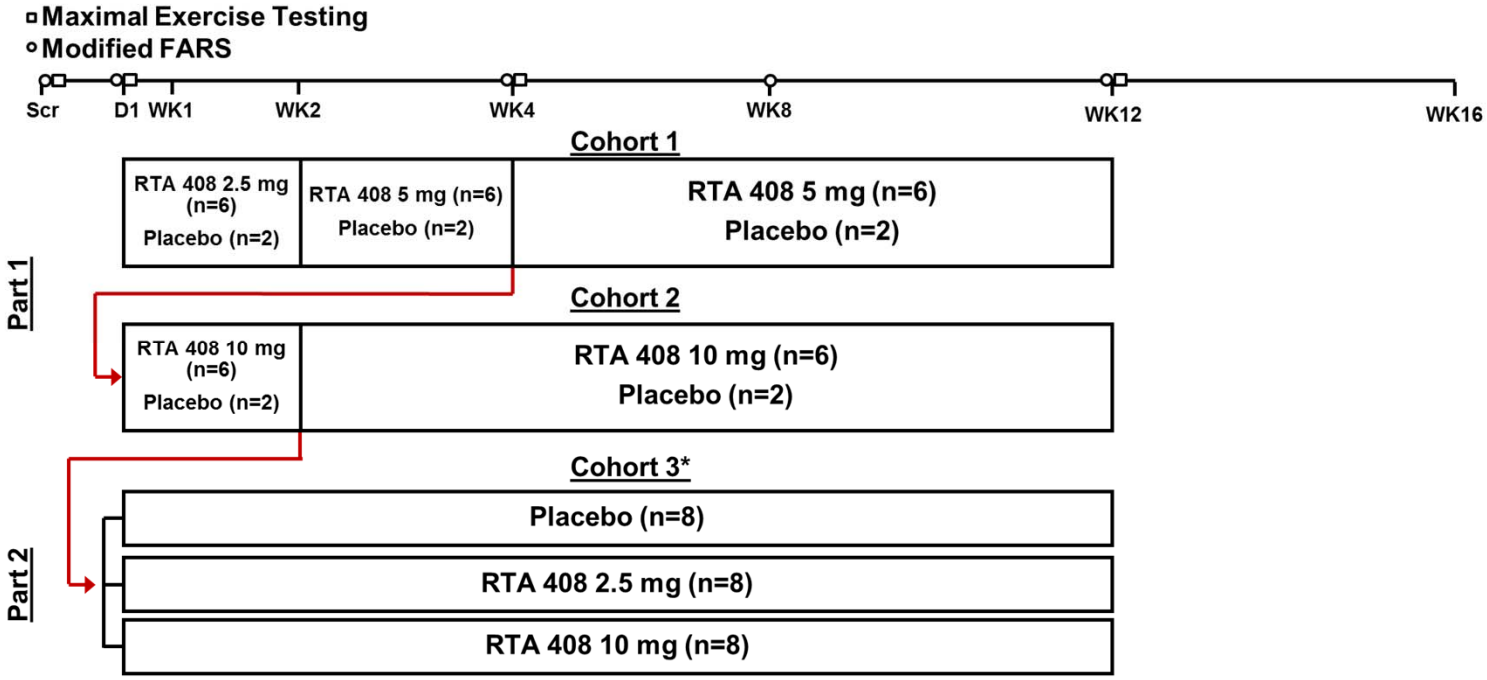
- Part 1: Randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg/5 mg and 10 mg
- Part 2: Randomized, placebo-controlled, double-blind, parallel study to evaluate safety, efficacy, and PD of two dose levels (2.5 mg and 10 mg) of RTA 408
- All patients follow the same visit and assessments schedule



Statistical Considerations

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Sample size for Part 2	24 patients (8 patients per treatment cohort)
Power	80%
Hypothesized Improvement	0.28 W/kg (assumes a common within-group SD of 0.28 W/kg)
Two-sided α	0.05
Sample size recalculation	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 (4 patients per treatment cohort)
Method of analysis	Change in peak work from Part 2 for patients treated with RTA 408 pooled (2.5 mg and 10 mg) compared to patients treated with placebo by repeated measures analysis of covariance

Study Sites and DSMB

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- Sites
  - CHOP/Penn – Dr. Lynch
  - University of Florida – Dr. Subramony
  - Emory University – Dr. Wilmot
  - Ohio State – Dr. Hoyle
- Independent, multidisciplinary DSMB monitoring this study along with a similarly designed study in mitochondrial myopathy patients (MOTOR)
  - DSMB includes a cardiologist, neurologist, statistician, and patient advocate
  - DSMB coordinated by an independent statistical group
  - Monthly meetings for safety oversight

Current Status

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- Part 1, Cohort 1 (n=8) enrollment completed in less than 2 months at a single site
  - All patients dose-escalated to 5 mg with no safety concerns
- Part 1, Cohort 2 (n=8) enrollment to open soon
- Monthly DSMB reviews underway with no identified safety issues
- Site activations nearly complete
  - 3 of 4 planned sites currently activated
  - 4th site expected to be activated by mid-April
- Part 2 (n=24 to 36) enrollment expected to begin in 2Q/3Q 2015
- Top-line data available 4Q 2015 or 1Q 2016

Thank You

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- Thanks to all investigators, site personnel, data safety monitoring board members, patients, and FARA who will and have been participating in the design and conduct of MOXIe

- Questions?