Title: A Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia

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PROTOCOL SYNOPSIS

Study Title	**A Phase 2a Study of NAD^+ Precursor Supplementation in Friedreich's Ataxia**
Funder	Friedreich's Ataxia Research Alliance (FARA)
Clinical Phase	Open Label, Safety and Tolerability
Study Rationale	Frataxin supports the function of the mitochondrial electron transport chain (ETC) because it facilitates the formation of iron-sulfur clusters, which are essential to multiple ETC components. Cardiac muscle has a high energy requirement, and the role of impaired mitochondrial oxidative phosphorylation capacity in the pathogenesis of FA-related cardiomyopathy is a focus of ongoing investigations. In animal models, there is evidence for disruption of the physiologic coupling between mitochondria and sarcomeres in cardiomyocytes, as well as iron accumulation and mitochondrial proliferation.[16] Similar phenomena may be observable in skeletal muscle in humans.[3,17] We hypothesize that MIB-626 therapy will be feasible, well-tolerated, and may increase cardiac mitochondrial bioenergetic capacity, as reflected by the phosphocreatine (PCr) to ATP ratio measured via cardiac ^{31}Phosphorus magnetic resonance spectroscopy (^{31}P- MRS).
Study Objective(s)	**Primary** • To test the safety and tolerability of short-term MIB-626 therapy in adults with FA without overt heart failure. **Secondary** • To use cardiac ^{31}P-MRS to measure the within-participant change in PCr/ATP-γ ratio before and after treatment with MIB-626. • To assess the within-participant change in skeletal muscle post-exercise CrCEST recovery (an index of skeletal muscle mitochondrial oxidative phosphorylation capacity) and the within-participant change skeletal muscle NAD^+ via 1H-MRS before and after treatment with MIB-626. • To assess within-participant changes in grip strength (via hand grip dynamometry) before and after treatment with MIB-626. • To measure the concentration of NAD^+ (and associated metabolites) in whole blood before and after treatment with MIB-626. • To assess within-participant change in the FARS-ADL, before and after treatment with MIB-626. • To assess within-participant change in overall well-being,

	assessed via CGI scales (CGI-S and CGI-C), before and after treatment with MIB-626.
Test Article(s)	MIB-626 two (2) 500 mg tablets, po daily
Study Design	Open Label, Single Arm, Assess Safety and Tolerability
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Molecular diagnosis of Friedreich's Ataxia (FA). 2. Males and females, ages 18y to < 65y. **Exclusion Criteria** 1. Known sensitivity to nicotinamide-containing compounds. 2. Concurrent use of vitamin B3 supplements and/or any medications likely to increase risk of MIB-626 toxicity. 3. HGbA1c $\geq$ 8.5% and/or DM requiring insulin or insulin secretagogue. 4. Kidney disease (eGFR < 60 ml/min/1.73 m^2) using serum creatinine and MDRD equation. The eGFR levels will be calculated using the MDRD (Modified Diet in Renal Disease study) equation, which is the equation used by the CHOP laboratory. 5. Liver disease (AST/ALT > 3x ULN) 6. Severe co-existing cardiac disease as manifest by a reduced LV ejection fraction to < 40%, moderate or greater valve disease, presence of a congenital heart defect, and/or evidence of pulmonary hypertension on an echocardiogram or cardiac MRI within 12 months of screening. 7. History of clinically significant arrhythmias (atrial fibrillation, atrial flutter, or ventricular tachycardia) or an increased potential for arrhythmias on the screening ECG as evidenced by: • Prolonged QTc (>480 ms for females or >460 msec for males) • Any rhythm other than sinus on the baseline ECG, excluding sinus arrhythmia. • Multiple PACs (>2) or PVCs on the baseline ECG 8. Prior history of heart failure. 9. Any contraindication to MRI, including spinal rods (related to unknown safety considerations for cardiac ^{31}P-MRS).

	10. Use of any investigational agent within 4 weeks of enrollment. 11. Females: Pregnant/lactating or planning to become pregnant during their participation. 12. Any medical condition that, in the opinion of the investigator, will interfere with the safe completion of the study.
Number Of Subjects	N =10 screened at CHOP with an aim to enroll and obtain complete data for 6 participants. 2 Sites: The Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania Study procedures will be completed at The Children's Hospital of Philadelphia and The Hospital of the University of Pennsylvania.
Study Duration	Each individual's participation will last up to 15 weeks.
Study Phases **Screening** **Study Treatment** **Follow-Up**	Participants will undergo a telephone screening to assess eligibility and then, within 90 days, complete an in-person screening to confirm eligibility. Participants with confirmed eligibility will be included and begin 14 (+/- 2) days of test article (MIB-626). Participants will complete a follow-up visit at the conclusion of 14 (+/- 2) days of MIB-626.
Efficacy Evaluations	PCr/ATP-γ ratio via cardiac ^{31}P-MRS Skeletal muscle CrCEST and NAD^+ (^{1}H-MRS) NAD^+ analysis of metabolites in whole blood Grip strength (hand grip dynamometry) FARS-ADL scale Clinician/participant clinical global impression (CGI) scales (CGI-S, CGI-C)
Safety Evaluations	Safety will be monitored through the collection of laboratory assessments at baseline and follow-up. Participants will also be monitored using a standardized assessment of symptoms (see attachment). We will use the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, U.S. Department of Health and Human Services) to grade adverse events. Individuals who experience a new Grade 3 or higher AE will be required to stop study participation.

Statistical And Analytic Plan	We will focus primarily on safety and tolerability. We will note the number of participants who complete the protocol, monitor adherence, and systematically collected adverse events. We will also use paired *t*-tests and/or Wilcoxon signed rank tests to assess within-participant changes in cardiac and skeletal muscle bioenergetics, NAD^+ metabolites, grip strength, FARS-ADL, and clinician/participant reported overall clinical status. To estimate statistical power, we used data from a previous study comparing cardiac ^{31}P-MRS assessments of tissue bioenergetics in individuals with FA as compared to control participants.[1] With an expected initial mean of adjusted PCr/ATP ratio in individuals with FA of 1.42 (SD 0.52) [1], and assuming a conservative short-term (i.e., over 14 (+/- 2) days) within-subject correlation of at least 0.6 between repeated measures, a sample of 6 individuals has 80% power to detect an improvement in PCr/ATP to 2.09 (normal = 2.20). This initial experience will generate estimates regarding the distribution of the candidate mechanistic/efficacy outcomes in FA and treatment responses, and may provide a basis for longer Phase 2/3 interventional studies of MIB-626 supplementation.
DATA AND SAFETY MONITORING PLAN	The PI is responsible for data quality management and continuous monitoring of study participants to ensure safety. Data will be reviewed at regularly scheduled team meetings. The PI and study team will report findings as required to the local Institutional Review Board and medical monitor.