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

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STATISTICAL CONSIDERATIONS

Primary Endpoint

The primary focus of this protocol is safety and tolerability. We will monitor participants using standardized assessment of symptoms and laboratory measurements.

Secondary Endpoints

Secondary endpoints will include the following:

- The within-subject change in PCr/ATP-γ ratio (^{31}P-MRS) before and after 14 days (+/- 2 days) of treatment with MIB-626.
- The within-subject change in post-exercise CrCEST recovery (CrCEST MRI) before and after 14 days (+/- 2 days) of treatment with MIB-626.
- The within-subject change in skeletal muscle NAD^+ (^{1}H-MRS) before and after 14 days (+/- 2 days) of treatment with MIB-626.
- The within-subject change in clinical global impression (CGI-S) scale before and after 14 days (+/- 2 days) of treatment with MIB-626. The CGI-C will be applied at the end of the study.
- To assess within-subject changes in the Friedreich Ataxia Rating Scale-Activities of Daily Living subscale (FARS-ADL) before and after treatment with MIB-626.
- The within subject change in hand grip strength (via dynamometry) before and after 14 days (+/- 2 days) of treatment with MIB-626.
- NAD^+ and its metabolites in whole blood before and after 14 days (+/- 2 days) of treatment with MIB-626.

Statistical Methods

Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

Efficacy Analysis

We will test for differences from zero of the key secondary outcome, the within-subject change in PCr/ATP-γ ratio, as well as other secondary outcomes of interest using paired *t*-tests and/or Wilcoxon signed rank tests, as appropriate given the variable distribution.

Safety Analysis

All participants entered into the study who receive the test article will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

Sample Size and Power

We propose a sample size of 6 participants with complete and evaluable data (we expect that we will verbally consent and telephone screen up to 10 participants).

Although the primary objective of the study is to assess safety and tolerability, we include here an estimate of statistical power for the key secondary endpoint of PCr/ATP-γ ratio. To estimate statistical power, we used data from a previous study comparing ^{31}P-MRS in individuals with FA as compared to control participants.[1] With an expected mean of adjusted PCr/ATP ratio of 1.42 (SD 0.52), and assuming a short term (i.e., over 14 days) within-subject correlation of 0.6 between 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 using this technique will generate estimates regarding the distribution of the cardiac ^{31}P-MRS outcomes in FA and may provide a basis for a longer phase 2/3 interventional study of NAD^+ precursor supplementation.

Interim Analysis

Due to the small sample size no interim efficacy or safety analyses is planned. Individuals who experience a new Grade 3 or higher AE will be required to stop study participation.