Original Title of Study: L-methylfolate supplementation to OROS-methylphenidate pharmacotherapy in ADHD Adults: A double-blind, placebo-controlled, randomized clinical trial.

NCT Number: NCT01853280

Date of SAP Plan: 12/22/2016

Deplin Statistical Analysis Plan – Paper 1

1. **General Analysis Details**
    a. Analyses will be intention to treat and include all subjects that received deplin or placebo for at least 1 week. We will perform a per protocol analysis as a secondary analysis.

2. **Demographic Characteristics & Baseline Efficacy Measures**
    a. We will compare demographic characteristics and baseline efficacy measures between those randomized to placebo and those randomized to deplin to ensure that the randomization process was successful.
        i. We will compare the groups using standard parametric and non-parametric tests (Student's t-test, Wilcoxon rank sum test, Pearson's chi-square test, Fisher's exact test).
        i. Demographic characteristics will include age, gender, race, and socioeconomic status.
        ii. Baseline efficacy measures will include AISRS, CGI, BRIEF-A GEC subscale, and GAF.

3. **Safety**
    a. Individual Adverse Events
        i. We will report a frequency table of recurrent adverse events. No statistical analyses will be performed on individual AEs.
    b. Total Number of Adverse Events
        i. We will compare the total number of AEs in each group using a Poisson regression model, which is the appropriate model for count data.
    c. Time-course of Adverse Events
        i. We will analyze the time-course of AEs using a mixed effects Poisson model that predicts the total number of AEs from the drug group, study week, and drug group x study week interaction. The interaction will tell us if there is a difference in the occurrence of AEs between the groups over the course of the study.
    d. Vitals
        i. We will analyze vital signs using mixed effects regression models with the drug group, study week, and drug group x study week interaction as predictors.

4. **Primary Efficacy Measure (AISRS)**
    a. We will analyze the AISRS using a mixed effects Poisson model that includes the drug group, study week, and drug group x study week interaction as predictors. Using this model is consistent with how we have analyzed the AISRS in previous publications.
        i. If there are statistically significant differences in demographic characteristics or baseline efficacy measures then we will add variables to the model to control for them.

5. **Secondary Efficacy Measures**
    a. Secondary outcomes measures will include the following: CGI, BRIEF-A, GAF, DESR, HAM-A, HAM-D, ASR, and CANTAB
        i. We will analyze the GAF and BRIEF-A using mixed effects Poisson models that include the drug group, study week, and drug group x study week interaction as predictors.
        ii. We will analyze the CGI using a mixed effects ordinal logistic regression model that includes the drug group, study week, and drug group x study week interaction as predictors.
        iii. For the DESR, HAM-A, HAM-D, ASR, CANTAB, and BRIEF-A, subjects will be define as having normal or abnormal scores based on pre-defined cutoffs from the literature. We will analyze these outcomes using mixed effects logistic regression models that include the drug group, study week, and drug group x study week interaction as predictors.

6. **Exploratory Analysis**
    a. We plan to examine the following biomarkers: MTHFR C677 CT/TT polymorphism, MTHFR A1298C polymorphism, FRa-autoantibody, and body mass index ≥ 30 kg/m^2
        i. Biomarkers are defined as typical or atypical based on standard values
        ii. We will use mixed effects Poisson models to test the three-way interaction between drug group, study week, and biomarker. The outcome of interest will be the AISRS.