ECHO AUTISM
Statistical Analysis Plan: Amendment 2

_____

Kristin Sohl, MD
University of Missouri
Study Chair

_____

Micah Mazurek, PhD
University of Virginia
Study Co-Chair

_____

Robert A. Parker, ScD
MGH Biostatistics Center

During preparation of a revision to the manuscript the team re-examined the basic model used for the analysis to ensure that it was adequately adjusting for time, as a referee had raised multiple questions about the analysis and expressed skepticism that a) our model was adequately adjusting for potential time factors and b) that the primary analysis should be the modified ITT population, not the completer population originally used.

Because of this the team prepared simulations to demonstrate to the reviewer that the analysis did appropriate adjustments for time trends. During this work it was discovered that the reviewer was indeed correct and that we had failed to adjust for time trends appropriately in the analysis. As such, the primary analysis was changed. This led to two changes in the SAP:

1. Change in Population and Model

The original text was:

10.3 Efficacy Analyses

10.3.1 Primary Efficacy Analyses

The primary efficacy analysis will be done in the completer population.

After imputation of missing data as described in Section 8.4, a generalized linear mixed model analysis will be used to predict the outcome (listed in Section 10.1, with details of how each variable is calculated and baseline is calculated) with the following fixed effects:

- period (cohort), a continuous variable from 1-5;
- time point (treated both as categorical variables [coded as "baseline", "3 months" and "6 months"] and as a continuous variable [coded as 0, 0.5, 1.0]; see below);

and the following random effects:

- site; and
- participant.

After the initial analysis, a final decision will be made as to whether the effect of time point should be treated as a categorical or a continuous variable. If the results suggest that there is a substantial benefit to treating time point as a categorical variable in at least one of the two co-primary outcome measures, then it will be retained as a categorical variable for all outcome measures; otherwise it will be treated as a continuous variable. For the purposes of this analysis, a substantial benefit is defined as a statistically significant improvement using a likelihood ratio test when time is treated as a categorical variable rather than a continuous variable. The decision in the primary efficacy analysis will be used in all other analyses.

Technical note: This model will use PROC GLIMMIX, and two random statements, one fitting a random intercept for site (RANDOM SITE) and one fitting a random intercept for PCP (RANDOM /subject = PCP). Note that although multiple imputation (PROC MIANALYZE) should work with PROC GLIMMIX results, there are reports of computational problems arising. Should

such problems arise in the analysis of the data from the study, the use of multiple imputation will be reconsidered.

and has been modified to:

10.3   Efficacy Analyses

10.3.1 Primary Efficacy Analyses

The primary efficacy analysis will be done in the modified ITT population

After imputation of missing data as described in section 8.4, a generalized linear mixed model analysis will be used to predict the outcome (listed in Section 10.1, with details of how each variable is calculated and baseline is calculated) with the following fixed effects:

- period, a categorical variable from 1-8;
- time point (treated both as categorical variables [coded as baseline, 3, 6, or 9 months] and as a continuous variable [coded as 0.5, 1.0]; see below); and

and the following random effects:

- site, as a random effect; and
- participant, as a random effect within site.

2.   Deletion of An Additional Analysis

Based on the change in population and reviewer comments, this section of the SAP was removed:

10.4   Effectiveness Analysis

The effectiveness analysis will repeat the efficacy analysis (Section 10.3) for the total population.