# A multicenter, randomized, double-blinded, placebo-controlled study of CYT107 to restore absolute lymphocyte counts in sepsis patients

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NCT02640807

**Final Statistical Analysis Plan**

All statistical analyses will be evaluated on an intent-to-treat basis. That is, data all patients who were enrolled in the study and received at least one dose of study drug were analysed. This corresponds to the safety dataset (SAF).

Comparisons across treatment groups at baseline will be performed using the Kruskal-Wallis test and Fisher exact test. To determine the effect of CYT107 on the incidence of ALC improvement by greater than 50% (primary outcome), and mortality, the Fisher exact test will be used. For secondary analyses, each outcome variable (e.g., absolute lymphocyte count) will be baseline adjusted by subtracting the corresponding baseline value. Baseline adjusted outcomes will then be analyzed using linear mixed-effects regression, adjusting for study day (as a categorical variable), treatment group, and the interaction between study day and treatment group. A study day-by-treatment group interaction will be used to quantify the differential effect of intervention over the course of the study, adjusting for baseline response. Study day will be treated as a quantitative factor and modeled using a four-knot natural spline. A random intercept indexed by study subject will be used to account for within-subject correlation among longitudinal measurements. The error variance will be allowed to vary by study day to account for heteroscedasticity. The combined treatment effect across all study days will be tested against the null hypothesis that the mean outcome is identical among groups at each study day. If the combined treatment effect across all study days meets the statistical significance threshold (0.05), a series of similar null hypotheses will be used to assess the combined treatment effect at each specific study day. These null hypotheses will be tested using a Wald-type multiple degree-of-freedom test. All tests will be evaluated at the 0.05 level, thus ensuring a type-I error rate of 5%. This method ensures that the family of comparisons across study days are adjusted such that the type-I error rate for the overall assessment of effectiveness of CYT107 on each outcome is preserved at 5%. No additional adjustments will be made to control the type-I error rate across different outcomes. Differences in means between treatment groups at each time point will be summarized using point estimates and the associated Wald-type 95% confidence intervals. In order to estimate the average difference in mean absolute lymphocyte count across the two CYT107 groups, relative to placebo, a secondary regression analysis will be implemented by combining low and high frequency CYT107 groups. Normal quantile-quantile plots of Pearson residuals and fitted-versus-residual plots will be examined to assess for deviations from residual normality or homoscedasticity, respectively. Transformations of baseline adjusted outcomes will be considered as necessary. All statistical analyses will be performed using the latest version of R (http://www.r-project.org).