Statistical Analysis Plan

SARS-CoV-2 Vaccination Strategies in Previously Hospitalized and Recovered COVID-19 Patients

Version 1
31 August 2023

NCT04969250

Analysis of Baseline Characteristics

Baseline characteristics of the four randomized groups in the 2x2 factorial trial will be summarized with summary statistics, including means (standard deviations), medians (25th, 75th percentiles), and percentages. Descriptive summaries of baseline characteristics will be carried out separately for those assigned an investigational agent in TICO and those assigned a placebo. Characteristics summarized will include baseline factors collected prior to randomization in TICO as well as follow-up data collected in TICO prior to randomization to the 2x2 factorial in VATICO.

Analysis of the Primary Efficacy Endpoint

Analysis will be intention to treat and include all participants including those assigned an investigational agent in TICO and those assigned a placebo in TICO. Quanterix antibody levels at VATICO baseline and at Weeks 12, 24, and 48 will be summarized with box plots by immediate/ deferred, by one/two doses, and by each arm in the 2x2 factorial.

For the comparison of Quanterix antibody levels at Week 48 (the primary endpoint), levels will be log10 transformed and evaluated with analysis of covariance that includes indicators for each factor of the factorial. An interaction test will be carried out between the two factors as well. The antibody level prior to randomization into VATICO, vaccination prior to enrolling in TICO, and assignment to an investigational agent in TICO will be included as covariates to reduce the residual standard error and improve efficiency of the primary comparisons.

Table 1. Power to detect various geometric mean ratios with n = 66 VATICO participants assuming residual standard error of 0.6787 estimated from AZ and MP TICO participants Quanterix antibody levels at baseline and 28 weeks.

	Geometric Mean Ratio					
	1.2	1.5	2.0	3.0	4.0	6.0
Power	7%	18%	43%	80%	94%	>99%

The log10 transformation will be undertaken as is conventional for NAb measurements (as the distribution of log responses is generally closer to a normal distribution), and then the estimates and confidence intervals will be anti-logged to provide estimates and confidence intervals for the ratio of GMRs. A GMR of one indicates that there is no difference between treatment groups in NAb response, for example, among participants who were randomized to immediate compared with those randomized to deferred vaccination. A GMR less than 1.0 provides indication of lower NAb response among those who received immediate compared to those who received vaccination deferred.

The percentage of participants with a 4-fold increase in antibody levels from baseline will be summarized for each factor in the 2x2 factorial using Mantel-Haenszel chi-square statistics.

These analyses will be repeated for participants randomized to an investigational agent in TICO and to a placebo in TICO. These analyses will also be repeated for the Quanterix antibody levels at Week 12 as well as at Week 24.

Analyses of Other Endpoints and Subgroups

Descriptive summaries will be reported for the composite safety outcome of grade 3 or 4 AE, SAE, or death for the one versus two dose strategy. Similar summaries will be reported for the one vs two dose strategies as well as for the immediate vs deferred strategies for the composite endpoint of SAE or death through Week 24. Non-adherence to the assigned vaccination schedule will be summarized similarly as well.

A number of additional subgroup analyses are planned for each treatment comparison, taking advantage of the data collected at baseline and during follow-up on TICO. Subgroup analyses for each primary objective and the comparisons of TICO active and placebo groups will be performed using regression analysis. In addition to subgroups according to the other factor in the factorial design and the randomization assignment in TICO, prior vaccination at entry to TICO, subgroups according to age, gender, race/ethnicity, geographic region, duration of infection at time of randomization, severity of infection as measured by the highest ordinal category experienced and time to sustained recovery, baseline antigen and antibody level in TICO, and baseline antibody level at the time of randomization to VATICO will be carried out. These analyses will be performed by including an interaction term with treatment in the regression model with the antibody level prior to randomization into VATICO included as a covariate.