1. Protocol summary

INSIGHT 016
Vaccination for Recovered Inpatients with COVID-19 (VATICO)

RATIONALE

The optimal timing and number of vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the ACTIV-3/TICO population (hospitalized due to COVID-19) has not been determined, and is the subject of scientific and ethical equipoise. The vaccines to be investigated in this study have been administered in unprecedented numbers to a broad population, have been carefully investigated and monitored, and are currently considered to be both generally safe and effective. COVID-19 infection is known to generally confer a period of SARS-CoV-2 immunity in most individuals, which would presumably be protective during the study specified period of deferral. COVID-19 infection is also thought to provide an adequate priming effect in most individuals, making the single vaccination arms that are part of this study a scientifically sound avenue for investigation, and ethical from a risk perspective.

DESIGN

In this Phase 4, open-label trial, participants of the ACTIV-3/TICO clinical trial at selected sites who received certain pre-specified blinded investigational agents or placebo as part of that trial, and who have since achieved sustained recovery, and who are still [TICO assignment] blinded, and who are still within 28 to 90 days after initial TICO randomization, will be randomized in this 2x2 factorial design to one of four groups:

(i) immediate versus 12 week deferral of first dose administration and also
(ii) one dose only, versus two doses to be given 4 weeks apart

of the Moderna mRNA-1273 or the Pfizer BNT162b2 vaccine (mRNA vaccines).

The primary objectives of this 2x2 factorial design are (i) to estimate the difference in neutralizing antibody (NAb) response to the mRNA vaccine from baseline to Week 48 among participants vaccinated early versus deferred, and (ii) to estimate the difference in NAb response to this vaccine among participants vaccinated once versus twice. The primary analyses will be carried out in participants randomized to placebo in TICO. Analyses will also be carried out for those who receive the investigational agent(s) studied in TICO.

A key secondary objective is to ascertain the effect, if any, of SARS-CoV-2 monoclonal antibodies, and other interventions that have been studied in hospitalised COVID-19 subjects, on natural and vaccine-induced immunity.

	Participants will be offered enrollment between 28 and 90 days after receiving select ACTIV-3/TICO investigational agents or placebo. The primary endpoint, immune response specific to the vaccination received, will be assessed at Week 48. Participants will have blood collected at time of enrolment, and at Weeks 12, 24 and 48 after study entry.
DURATION	48 weeks.
SAMPLE SIZE	Approximately 640 participants. The total sample size will depend on how many select investigational agents/placebo are evaluated in ACTIV-3/TICO.
POPULATION	ACTIV-3/TICO trial participants at selected sites who received certain investigational agents or placebo 28 to 90 days previously, and have experienced sustained recovery for two or more weeks, and have not yet been vaccinated post COVID-19 illness.
REGIMEN	One or two (given approximately 4 weeks apart) injections of either the 100 µg Moderna mRNA-1273 vaccine or the 30 µg Pfizer BNT162b2 vaccine, given intramuscularly. Choice of vaccine is determined based on availability at the site. The choice is individual, although participants vaccinated twice should receive the same type of vaccines for both injections. The first vaccination is given either immediately after enrolment in this protocol or deferred for 12 weeks.
STRATIFICATION	Randomization to one of the 4 treatment groups will be stratified by study site pharmacy and investigational agent assignment in TICO.
MONITORING	An independent data and safety monitoring board (DSMB) will review interim safety data on a regular basis. The DSMB will be the same DSMB that reviews ACTIV-3/TICO agents.