1 Protocol Summary

DESIGN

TICO (Therapeutics for Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or directly enhancing viral control in order to limit disease progression.

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol.

The international trials within this protocol will be conducted in several hundred clinical sites. Participating sites are affiliated with networks funded by the United States National Institutes of Health (NIH) and the US Department of Veterans Affairs.

The protocol is for a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control (i.e., placebo + SOC) within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomly allocated across agents (as well as between the agent and its placebo) so the same control group will be used, when feasible. Randomization will be stratified by study site pharmacy and disease severity. There are 2 disease severity strata, defined as below:

Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

The primary endpoint is the time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days prior to Day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

An independent Data and Safety Monitoring Board (DSMB) will regularly review interim analyses that summarize safety and efficacy outcomes. For agents with minimal pre-existing safety knowledge, the pace of enrollment will be initially restricted and there will be an early review of safety data by the DSMB. For the study of all agents, at the outset of the trial, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 300 participants are enrolled and followed for 5 days. The exact number will vary according to the speed of enrollment and the timing of DSMB meetings. Prior to expanding enrollment to also include patients in disease severity stratum 2 safety will be evaluated and a pre-specified futility assessment by the DSMB will be carried out using 2 ordinal outcomes (see below) assessed at Day 5. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest (worst) category that applies on Day 5 will be assigned. This outcome is referred to as the "pulmonary" ordinal outcome, with categories described below:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, also assessed at Day 5, captures the range of organ dysfunction that may be associated with progression of Coronavirus-Induced Disease 2019 (COVID-19), such as stroke and other coagulation-related complications. Again, the highest category that applies on day 5 will be assigned. Use of this outcome allows further characterization of the extra-pulmonary manifestations of COVID-19 and the capacity to identify agents that improve those extra-pulmonary manifestations. This outcome is referred to as the "pulmonary+" ordinal outcome.

The 7 categories of the pulmonary+ ordinal outcome assessed at Day 5 are:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset congestive heart failure (CHF) NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacement therapy
7. Death

Both ordinal outcomes are used to assess futility because it is currently unclear whether the investigational agents under study will primarily influence non-pulmonary outcomes, for which risk is increased with SARS-CoV-2 infection, in part, through mechanisms that may be different from those that influence pulmonary outcomes.

For investigational agents passing this futility assessment, enrollment of participants will be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1. Future interim analyses will be based on the primary endpoint of sustained recovery and will use pre-specified guidelines to determine early evidence of benefit, harm or futility for the investigational agent.

DURATION

Participants will be followed for 18 months following randomization. Primary and most secondary outcomes will be collected during the first 90 days of follow-up only. Follow-up beyond 90 days is planned because the half-lives of some agents indicate that potentially meaningful amounts may remain in the body after 90

days of follow-up. During the follow-up between 90 days and 18 months hospitalizations and deaths will be ascertained.

SAMPLE SIZE — This phase III trial is planned to provide 90% power to detect a 25% increase in the rate of sustained recovery for an investigational agent compared to placebo at the 0.025, 1-sided level of significance. This requires 843 primary events (i.e., participants who achieve sustained recovery). Randomization of 1,000 participants, equally allocated to each investigational agent and placebo, followed for 90 days is estimated to result in the required number of primary events. The event target may be achieved earlier if more than 1,000 participants are enrolled. Sample size will be evaluated periodically by study team members who are blinded to interim results and may be increased to maintain power for the hypothesized difference in sustained recovery between the investigational agent and placebo.

POPULATION — The study population consists of inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days. Initially, approximately 300 participants in disease severity stratum 1 will be enrolled. Afterwards, based on the review by the DSMB of safety and futility, eligibility for randomization will be expanded to also include patients in disease severity stratum 2.

STRATIFICATION — Randomization will be stratified by study site pharmacy and also by disease severity stratum.

REGIMEN — Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data demonstrating activity against SARS CoV-2 entry or replication, preclinical data, phase I pharmacokinetic and safety data, and clinical data from other ongoing trials. The protocol will initially focus on agents for which there is a hypothesized benefit from passive immunization including use of neutralizing monoclonal antibodies.

MONITORING — An independent DSMB will review interim data on a regular basis and use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome, and if so recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

For an investigational agent, if the trial is stopped early or if the trial continues until the pre-specified number of primary endpoints is reached, further enrollment of the investigational agent will be terminated if applicable, and the trial data for the investigational

agent will be unblinded and reported with data through 90 days of follow-up. Follow-up of all participants will continue through 18 months using the data collection plan described in this master protocol.

A risk-based protocol monitoring plan will be developed to ensure participant safety, data integrity, and regulatory compliance during the conduct of the trial.