1 Protocol Summary

DESIGN

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with acute respiratory failure related to COVID-19. The focus in this master protocol, a sister protocol to the TICO master protocol, is on patients with critical respiratory failure (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO to treat acute hypoxemic respiratory failure caused by SARS-CoV-2 pneumonia).

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. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

The international trials within this protocol will be conducted in up to 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 within the same trial infrastructure. When more than one agent is being tested concurrently, participants may be randomly allocated across agents (as well as between the agent and its placebo) so the same control group can be shared, when feasible. In some situations, a factorial design may be used to study multiple agents.

The primary endpoint is a 6-category ordinal outcome that assesses the recovery status of the patient at Day 90. The categories of the ordinal outcome, from best to worst, start with 3 categories of “recovery” defined by the number of days alive at home and not on new supplemental oxygen, followed by 3 categories for “not recovered” defined as a) discharged but not to home or at home but still requiring continued new supplemental oxygen, b) hospitalized or receiving hospice care, and c) death at 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.

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) Master Protocol
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DURATION	Participants will be followed for 90 days following randomization for the primary endpoint and most secondary endpoints. Selected secondary endpoints will be measured at 180 days.
SAMPLE SIZE	This Phase III trial is planned to provide 80% power to detect an odds ratio of 1.5 for improvement in recovery status at Day 90 for an investigational agent versus placebo with use of the ordinal outcome. The planned sample size is 640 participants (320 per group) for each investigational agent / placebo. Sample size may be re-estimated before enrollment is complete based on an assessment of whether the pooled proportions of the outcome are still consistent with adequate power for the hypothesized difference measured by the odds ratio.
POPULATION	All participants enrolled will include inpatient adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO at enrollment, in whom the current respiratory failure is thought to be due to SARS-CoV-2 infection and in whom respiratory support was initiated within 4 days prior to randomization.
STRATIFICATION	Randomization will be stratified by study site pharmacy and by receipt of invasive mechanical ventilation or ECMO at enrollment. Other agent-specific stratification factors may be considered.
REGIMEN	Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data, preclinical data, phase I pharmacokinetic and safety data, and clinical data from completed and ongoing trials. In some cases, a vanguard cohort/initial pilot phase may be incorporated into the trial.
MONITORING	An independent DSMB will review interim safety and efficacy data at least monthly. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm or substantial efficacy. The DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits.