## 1.1 Synopsis

### 1.1.1 Rationale for Proposed Clinical Study

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. This novel coronavirus has been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus has been designated coronavirus disease 2019 (COVID-19). There were 59 confirmed cases on January 5, 2020, 2118 cases on January 26, 2020, rising to more than 20 million confirmed cases and 750,000 deaths as of August 16, 2020 according to various international health reporting agencies.

Hyperimmune intravenous immunoglobulin (hIVIG) to SARS-CoV-2, derived from the plasma of individuals who recover and develop neutralizing antibodies, is a potentially useful therapeutic approach to COVID-19. Augmentation of the humoral immune (antibody) response using passive immunotherapy with hIVIG to SARS-CoV-2 at the onset of clinical progression before end-organ failure has developed may reduce the subsequent risk of further disease progression and death.

### 1.1.2 Study Design

This protocol will serve as a platform for assessing treatments for adult patients hospitalized for medical management of COVID-19 without related serious end-organ failure. Trials will involve sites around the world strategically chosen to ensure rapid enrollment. Initially, this trial will compare hIVIG with matched placebo, when added to standard of care (SOC), for preventing further disease progression and mortality related to COVID-19. SOC will include remdesivir unless it is contraindicated for an individual patient.

In future versions of the protocol, one or more drugs from a different class and with different mechanisms of action may be studied. Such treatments could be studied along with hIVIG if it is found effective and safe in this initial version of the protocol.

The primary endpoint of this trial in hospitalized patients is an ordinal outcome based on the patient's clinical status on Day 7. It includes 7 mutually exclusive categories capturing the range of organ dysfunction that may be associated with progression of COVID-19, such as respiratory dysfunction and coagulation-related complications (see Appendix F for full definition):

7. Death

6. End-organ failure

5. Life-threatening end-organ dysfunction

4. Serious end-organ dysfunction

3. Moderate end-organ dysfunction

2. Limiting symptoms due to COVID-19

1. No limiting symptoms due to COVID-19

Secondary endpoints include time to the 3 least favorable categories, time to the 2 most favorable categories, and the pulmonary only and thrombotic only components of the primary ordinal outcome. Mortality, adverse events (AEs), including infusion reactions, and biological correlates of therapeutic activity are also assessed. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups (initially hIVIG + SOC versus placebo + SOC) can be compared for multiple outcomes, and results can be compared or combined with other trials.

Participants will be randomized (1:1) to a single infusion of hIVIG + SOC or placebo + SOC on the day of randomization (Day 0). Participants taking remdesivir prior to randomization may be enrolled if eligibility criteria are met. Randomized participants who were not taking remdesivir before randomization will start taking remdesivir immediately following the infusion of hIVIG or placebo unless remdesivir is contraindicated. Participants will be followed for 28 days and, if the trial goes to completion, the primary analysis will be completed after all participants are followed for 28 days.

The planned sample size is 500 participants (250 per group). After 150 participants are enrolled, sample size will be re-estimated, by investigators who are blinded to interim treatment results using pooled outcome data.

The study population will include consenting hospitalized patients with COVID-19 who have had COVID-19 symptoms ≤ 12 days, and who do not have life-threatening organ dysfunction or organ failure.

Many other clinical trials evaluating treatments for COVID-19 are either ongoing or being planned. If findings from another trial have implications for the design and

conduct of this trial, the protocol may be modified depending on the strength of the trial results and the target population studied.

An independent Data and Safety Monitoring Board (DSMB) will review interim data and use pre-specified guidelines for early termination of the trial or protocol modification. The DSMB will also be consulted concerning protocol modifications for reasons described above (e.g., sample size re-estimation or other aspects of the design resulting from emerging data). All protocol modifications will be discussed with the independent DSMB. Protocol amendments will be submitted to ethics committees (ECs) and a central institutional review board (IRB) in the United States of America (US).

After consent and eligibility has been determined, a single infusion of hIVIG or placebo will be administered on the day of randomization (Day 0). Remdesivir infusions will follow the hIVIG/placebo infusion. Any infusion reactions and interruptions of the planned hIVIG/placebo infusion will be recorded. The ordinal outcome will be assessed throughout follow-up, including on Day 7 for the primary endpoint. On Day 0 (pre-hIVIG/placebo infusion), and on Days 1, 2, 3, 7, and 28, a blood sample will be obtained to centrally measure neutralizing antibody levels along with total immunoglobulin G (IgG) concentrations and its subclasses, immunoglobulin A (IgA), and immunoglobulin M (IgM); for participants at selected sites an additional blood sample for these measurements will be obtained at Day 90. Serious Adverse Events (SAEs), including deaths from any cause, will be collected through Day 28. hIVIG infusion related events of any grade will be collected. Grade 3 and 4 AEs will be collected through Day 7. AEs of any grade experienced on Days 1, 3, 7, and 28 will be recorded.