COVIDOSE-2: A multi-center, randomized, controlled phase 2 trial comparing early administration of low-dose tocilizumab to standard of care in hospitalized patients with COVID-19 pneumonitis who do not require invasive mechanical ventilation

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Study Design: A multi-center randomized, controlled phase 2 trial studying the use of reduced-dose tocilizumab for COVID-19 compared to that of standard of care treatment.

Eligible Patients: Hospitalized patients with a diagnosis of COVID-19 pneumonitis

Primary Objectives:

1. To establish whether low-dose tocilizumab reduces the time to clinical recovery in patients with COVID-19 pneumonitis and hyperinflammation.

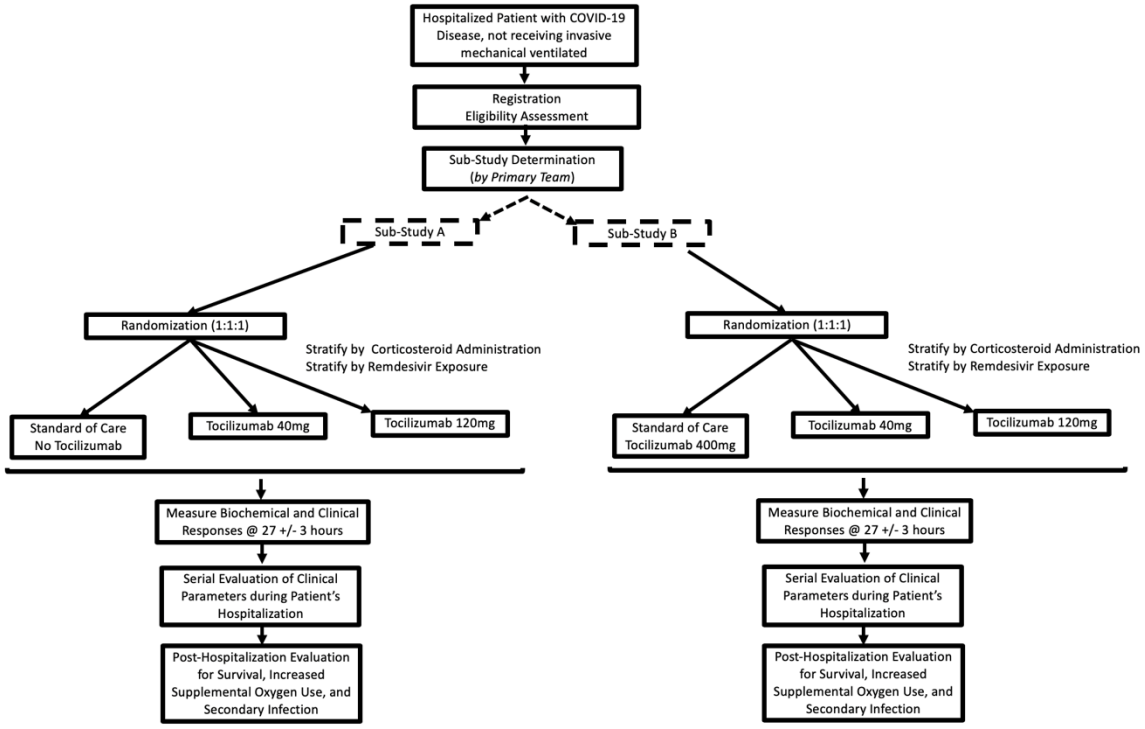
Secondary Objectives:

1. To establish whether low-dose tocilizumab increases the probability of clinical recovery at seven days in COVID-19 pneumonitis.

2. To establish whether low-dose tocilizumab decreases signs, symptoms, and laboratory evidence of COVID-19 pneumonitis.

To compare the survival, hospital length of stay, rate of progression of COVID-19 pneumonitis, rate of non-elective mechanical ventilation, number of days to mechanical ventilation, number of days requiring mechanical ventilation, rate of vasopressor support utilization, number of days to vasopressor support, number of days of vasopressor support, and duration of supplemental oxygen requirement higher than prior to hospitalization in non-critically ill patients with COVID-19 pneumonitis who receive either standard of care treatment (incorporating either no tocilizumab at all or higher-dose tocilizumab (equalling 400mg or 8mg/kg)), low-dose tocilizumab 40mg, or low-dose tocilizumab 120mg.

OVERALL STUDY SCHEMA:



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INTRODUCTION

1.1 Background and Rationale

1.1.1 COVID-19 and Global Pandemic

The global pandemic of coronavirus disease-2019 (COVID-19), secondary to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), represents an emergent threat to public health, with a quoted mortality rate among inpatients greater than 15%.[1] Containment strategies have been employed to varying degrees and effects in Western nations, now necessitating mitigation strategies in overwhelmed hospitals to effectively address COVID-19. Limited intensive care unit- (ICU) level resources such as mechanical ventilation and other in-hospital resources such as bedding space have played a significant role in the poor clinical outcomes associated with COVID-19.[2-4] Moreover, the throughput and length of hospitalization of patients requiring acute care beds may play a role in the "logjam" of available resources in a pandemic.[5,6] Therefore, early identification of patients at risk for clinical decompensation, imminently preventing their decompensation so as to preserve as many ICU-level resources as possible, and decreasing the length of stay of non-critically ill patients are all crucial at a public health level to navigate the COVID-19 pandemic.

Local efforts to control the COVID-19 pandemic have been heterogeneous within the United States, such that many communities are experiencing "second waves" associated with re-opening strategies and/or insufficient containment measures. Perhaps more accurately, the "first wave" was either never experienced or never went away and instead the current state is either an elevated plateau or a community's first real wave. In either case, the urgency of the pandemic on a national and to an extent global scale has not abated and therapies are urgently needed.

1.1.2 Risk of Death in COVID-19 Disease

COVID-19 pneumonitis exists on a continuum, ranging from (on one extreme) bilateral infiltrates and associated respiratory failure, hyperinflammation, and septic shock leading to death to (at the other extreme) absence of pulmonary infiltrates and very mild symptoms. For the purposes of this study, patients meet diagnostic criteria for COVID-19 pneumonitis when they have: 1) positive SARS-CoV-2 viral polymerase chain reaction test and 2) evidence of an infiltrate on chest imaging. Those patients with COVID-19 disease who do not have pulmonary infiltrates are generally at low risk for progression to pneumonitis and clinical decompensation, ICU resource utilization, and death.[7]

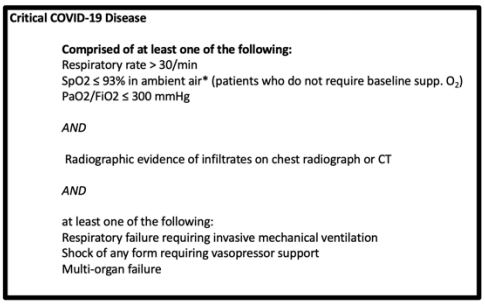

Figure 1. Clinical and radiographic characteristics of patients with Critical COVID-19 disease.

For the purposes of the previous COVIDOSE study (IRB20-0515), hereafter referred to as COVIDOSE-1 to differentiate it from the proposed study, we focused on hospitalized patients with signs of COVID-19 pneumonitis who were not designated to be "critically ill," as delineated by aforementioned parameters (Figure 1). Based on previously published data,[8] these remaining hospitalized patients with COVID-19 pneumonitis have risk of

clinical decompensation, intensive care utilization, and COVID-19-related mortality. These patients may benefit from early treatment with medications aimed at managing COVID-19 disease-related CRS. As a public health measure, early treatment may help to preserve limited ICU resources.

1.1.3 COVID-19 Mortality and Limited Promise of Antiviral Agent Remdesivir Monotherapy

Repurposed investigational therapies to this point have been divided into antiviral therapies such as hydroxychloroquine, lopinavir/ritonavir, and remdesivir and adjunctive anti-inflammatory therapies, including hydroxychloroquine, Janus kinase (JAK) inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, immunomodulating biologics such as anakinra and immunosuppressive monoclonal antibodies.[9] In the preliminary report of the Adaptive COVID-19 Treatment Trial (ACTT),[10] authors showed remdesivir, the most promising antiviral to date, was statistically superior to placebo in reducing hospitalized adults' recovery time by a clinically relevant four days (on an ordinal scale of disease severity).[10] Although clinically meaningful, the hazard ratio for death with remdesivir treatment was 0.70, a result that was not statistically significantly at a threshold p-value of 0.05. While the overall survival result may eventually be demonstrated to be substantial, the inability of a pharmacologically active antiviral therapy to clearly reduce COVID-19 disease's high mortality suggests additional therapeutic approaches may be important, particularly in those patients with more severe disease.[10]

1.1.4 Dexamethasone in COVID-19

Recent evidence demonstrates the benefit of dexamethasone in the treatment of hospitalized patients with COVID-19. This trial, the RECOVERY trial from the United Kingdom, randomized hospitalized patients with COVID-19 of all levels of severity, 2104 in total, to receive either dexamethasone 6mg daily for up to ten days or to usual standard care.[11] Arms were well balanced between the two treatment assignments, with dexamethasone patients being statistically older than those receiving usual standard of care. Those patients receiving dexamethasone had statistically lower probabilities of 28-day mortality and receipt of invasive mechanical ventilation, with higher probability of discharge from hospital within 28 days.[11] Subgroup analysis demonstrated that the effects may have been most profound in patients receiving supplemental oxygen and invasive mechanical ventilation. On the basis of this evidence, it is likely that, similar to acute respiratory distress syndrome, steroids are beneficial in the latter stages of COVID-19.

Steroids, especially in the context of concurrent infection and high risk for secondary infection, are not benign medications. Not reported, but of concern, include secondary opportunistic and bacterial infections as well as the role of dexamethasone on the development of anti-Spike and anti-RBD antibodies against SARS-CoV-2. Experience during the initial wave of SARS in the early 2000s raised additional questions with respect to steroid use. Diminished bone health, namely avascular necrosis, from prolonged steroid use emerged as a significant risk during the SARS epidemic.[12,13] Short- and long-term steroid-related risks of adrenal insufficiency and diabetes mellitus have also been raised during the COVID-19 pandemic.[14,15] Taken together, these emerging data when viewed in the context of the clear proof-of-principle for reduction of

inflammation in COVID-19 established by the RECOVERY trial demonstrate a clear need for steroid-sparing immunomodulatory treatment strategies.

1.1.5 Parallels Between COVID-19 and Chimeric Antigen Receptor T-Cell (CAR-T)- Related Cytokine Release Syndrome (CRS)

Instead, COVID-19's high mortality may in part be driven by hyperinflammation resembling the cytokine storm often identified in hemophagocytic lymphohistiocytosis and cytokine release syndrome (CRS), offering the hope that immunosuppressive therapies commonly used to treat CRS – such as the interleukin-6 (IL-6) receptor-targeted monoclonal antibodies tocilizumab or sarilumab and IL-6 targeted monoclonal antibody siltuximab – can be used to reduce mortality in COVID-19 (Figure 2).[16] Emerging evidence shows marked elevation of serum IL-6, C-reactive protein (CRP), lactic dehydrogenase, and ferritin in patients with COVID-19, with the degree of elevation correlating with severity of disease.[8,17,18] Early data suggest IL-6 axis suppression has promise. Retrospective analysis of severe to critical COVID-19 patients receiving tocilizumab 400 mg (approximately 6.67 mg/kg using average Chinese body weight) demonstrated that greater than 75% of patients had rapid resolution (i.e., within 24-72 hours following administration) of both clinical and biochemical signs (fever and CRP, respectively) of hyperinflammation with only a single tocilizumab dose.[18]

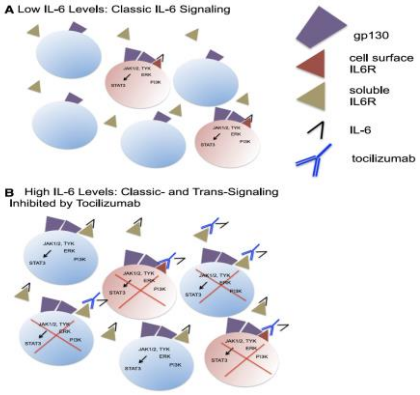

Figure 2. Interleukin-6 signaling in cytokine release syndrome (CRS) in chimeric antigen receptor T-cell (CAR-T). In normal circumstances (panel A), classic IL-6 signaling, marked by IL-6 binding only to cell-bound IL-6 receptors (IL-6R), predominates. IL-6-axis signaling typically only occurs in neutrophils, macrophages, hepatocytes, and select T-cells. Under circumstances such as CAR-T-mediated CRS (B) and possibly COVID19-mediated CRS, IL-6 levels are markedly elevated, leading to pro-inflammatory *trans* IL-6-axis signaling and resultant systemic inflammation akin to sepsis. (Image first published in Lee *et al*, Blood, 2014. Legend is independently written.)

Although prospective trials or even large retrospective trials are scant and peer-reviewed literature otherwise on the topic is still scarce, what has been gleaned thus far is illuminating. First, a randomized, controlled trial conducted at multiple institutions in France has, per press release, shown promising signs of tocilizumab's efficacy in COVID-19 treatment.[19] Sanofi/Regeneron has released results of phase 2/3 studies of sarilumab in COVID-19, with clear signs of clinical benefit in the high-dose sarilumab arm of the study.[20] Real-world evidence of off-label tocilizumab use also point to its benefit.[21]

1.2 Tocilizumab

1.2.1 Clinical Studies

Tocilizumab was originally developed for outpatient, every four-weeks administration in rheumatoid arthritis (RA), giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis at a labeled dose of 8 mg/kg, with approval

based on improvement in the American College of Rheumatology (ACR) 20 score.[22] Dose-finding studies revealed a dose-related reduction in Disease Activity Score in 28 joints (DAS28) beyond 4 weeks at doses 4mg/kg and 8mg/kg.[22]

In its subsequent new drug application for treating CRS in chimeric antigen receptor T cell (CAR T) therapy, no formal dose-finding study was performed and tocilizumab was approved after the 8mg/kg dose, provisioned up to four times at least eight hours apart, led to resolution of CRS within a 14-day period of time (the primary outcome measure for these purposes).[22] Response data from Food and Drug Administration (FDA) filings, however, suggest a 4 mg/kg dose had similar efficacy (table 18).[23] Critically, lower doses were not studied.[23] No common CRS biomarkers such as ferritin or C-reactive peptide (CRP) response were included as part of tocilizumab's FDA filings.[23] The FDA's own review stated: "It was notable that some patients in the Treated Population had resolution of CRS by day 14 after receiving tocilizumab 4 mg/kg, suggesting that a dose lower than recommended might be effective".[23]

New information suggests a role for tocilizumab in COVID-19 pneumonitis and the related CRS. A French multicenter randomized, controlled trial of tocilizumab 8mg/kg in hospitalized patients with COVID-19 reportedly has demonstrated "significant" clinical benefit in patients when compared to standard of care.[19] Additionally, the IL-6R-targeted monoclonal antibody sarilumab has shown signs of efficacy in an early industry-sponsored phase 2/3 study.[20]

Additional evidence derived from platform randomized controlled trials has demonstrated *mortality* benefit with tocilizumab.[24,25] Consequently, tocilizumab has been adopted as a standard of care treatment in many parts of the industrialized world, including the United Kingdom, Canada, and European Union, for patients with incipient organ failure or within 24 hours of admission to an intensive care unit and elevated C-reactive protein.

1.2.2 Drug Shortages in the Treatment of COVID-19

Even if immunosuppressive monoclonal antibodies are efficacious therapies, challenges remain. As in the case of hydroxychloroquine, aggregate demand for anti-IL6 therapies driven by off-label utilization could quickly outstrip available supplies.[26,27] Moreover, the supply of these anti-IL6 therapies may not be efficiently matched to hospitals expected to bear the brunt of COVID-19.[28] To overcome the drug supply/demand mismatch, three challenges must be overcome: 1) demand must be reduced through maximal containment measures, 2) the available medication's distribution channels must be improved, and 3) the *effective* supply of the medications must be increased by increasing manufacturing and extending the extant anti-IL-6 therapy as much as possible.

1.2.3 Risk of Bacterial Infection in Patients with COVID-19 Treated with Tocilizumab

There is medical rationale for low-dose tocilizumab in COVID-19.[29] In the early era of COVID-19 treatment, there was concern that immunosuppression for long periods of time of patients expected to have long inpatient hospital stays would increase the risk of nosocomial infection or bacterial superinfection, both of which have been concerns in patients with coronavirus infections.[30-32] Retrospective studies in the COVID-19 space

have validated these concerns. Single-center retrospective studies have estimated an approximately three-fold increase in the likelihood of secondary bacterial infections (e.g., hospital acquired and ventilator associated pneumonias) in patients receiving tocilizumab at higher doses.[32,33] Higher rates of infection were not identified in large-scale platform randomized controlled trials.[25]

Lower doses of tocilizumab, with consequent lower peak concentration and shorter duration of immunosuppression, may reduce the frequency and the duration of these adverse events.[29] In the initial COVIDOSE-1 study, the observed rate of secondary bacterial infection (e.g., ventilator-associated pneumonia, hospital acquired pneumonia, or bacteremia) in patients treated with low-dose tocilizumab was approximately one-fourth that of mechanically ventilated patients who received tocilizumab approximating the labeled dose.[33,34] There may still be a marginal increase in the risk of nosocomial pneumonia even with low-dose tocilizumab – the likelihood of COVIDOSE-1 patients developing serious bacterial infections was approximately equal to that of mechanically ventilated patients not treated with tocilizumab.[33] How the rates of prospectively-collected secondary infections compare between low-dose tocilizumab-, high-dose tocilizumab (400 mg or 8 mg/kg)-, and dexamethasone-treated patients and their respective control populations remains to be seen,[11] and carefully conducted prospective studies with appropriate biological correlates are much needed in this space.

1.2.4 **Interventional pharmacoeconomics to increase effective supply**

We can draw on lessons from the new field of interventional pharmacoeconomics (IVPE) to increase the effective supply of anti-IL-6 therapy.[35] Many monoclonal antibodies used in both oncologic and rheumatologic indications in the *outpatient* setting have labeled doses and schedules aimed at maintaining a therapeutic concentration for weeks. In contrast, in the inpatient setting, where a patient's primary problem is expected to be temporary and on the order of days, a lower and more frequent dosing of a monoclonal antibody is preferable. This approach helps to minimize the total amount of medication used and reduce the frequency and/or duration of adverse events. This pharmacological line of reasoning is germane to COVID-19 and is a plausible strategy to conserve use of potentially efficacious and supply-limited anti-IL6 therapies. Extrapolating from IVPE as applied to cancer, extending the supply of expensive medications is a particularly useful tactic in low- and middle-income countries (LMICs) as well as rural hospitals.[36] These localities are also expected to bear the brunt of COVID-19's impact.

1.2.5 **A Treatment Strategy Incorporating Low-Dose Tocilizumab**

At an individual patient level, utilizing a practical and effective low dose of a drug can optimize efficacy while minimizing adverse events. On a more global scale, the logic behind a grand strategy for COVID-19 pandemic mitigation efforts is to proactively utilize one rare resource (tocilizumab) to prevent utilization of another, more limited resource (ICU-level care). The goal of the overarching treatment strategy is to provision potentially efficacious therapy to the greatest number of patients likely to benefit from tocilizumab while still preserving an adequate supply for critically ill patients (Figure 3).[27] Tocilizumab's effectiveness in CRS after CAR-T therapy has led to off-label treatment of CRS from COVID-19 infections with preliminary evidence showing efficacy.[37]

As with most drugs, tocilizumab baseline supply is matched to baseline demand. In the presence of a rapid increase in anticipated demand due to a global pandemic, it is unclear if supply could be efficiently increased to match said demand in time to be useful.[34] Roche has increased tocilizumab production, but this production has been for the sake of global clinical trials.[38] Thus, relative to anticipated demand, tocilizumab is in limited supply both domestically and globally.[34,39] In this context, we proposed the development of alternative treatment regimens to address COVID-19-related hyperinflammation with the aim of providing therapy for the greatest number of patients likely to benefit.[29]

We estimate *a priori* that a target maximum concentration of tocilizumab likely to provide biochemical response as well as clinical benefit for patients with COVID-19 is approximately 8μg/mL.[29] Given the much lower IL-6 concentrations in COVID-19 compared to CAR-T-related CRS, we hypothesized that single doses less than 400 mg would be effective.[17,40] In the initial COVIDOSE-1 study, clinical and biochemical responses were observed in patients receiving as low as 40mg of tocilizumab, providing proof-of-principle for the approach. A minimum effective dose was not identified, but a practical and effective low dose of 40mg – representing one-half of tocilizumab's smallest vial size and approximately 10% of the currently accepted standard COVID-19 dose – was.

1.2.6 Dose-finding Studies for Tocilizumab in COVID-19

To our knowledge COVIDOSE-1 was the first dose-finding study to be completed for tocilizumab in COVID-19 disease or CAR-T-related CRS. COVIDOSE-1 succeeded in identifying a practical and potentially effective low dose of tocilizumab for the treatment of COVID-19 pneumonitis.

Preliminary Data from the COVIDOSE-1 Trial

In exploring lower doses of tocilizumab, we initially stratified patients on the basis of their perceived risk of clinical decompensation due to COVID-19 for the purposes of safety. Patients not meeting definition of critical COVID-19 (Figure 1) were divided into Group A (patients with COVID-19 disease who have known epidemiologic risk factors) as shown in Figure 3 and biochemicalevidence of incipient hyperinflammation as determined by a pre-designated adjudicated CRP level of ≥ 75μg/ml) and Group B, patients with COVID-19 disease who do not have these known epidemiologic risk factors or evidence of incipient hyperinflammation.

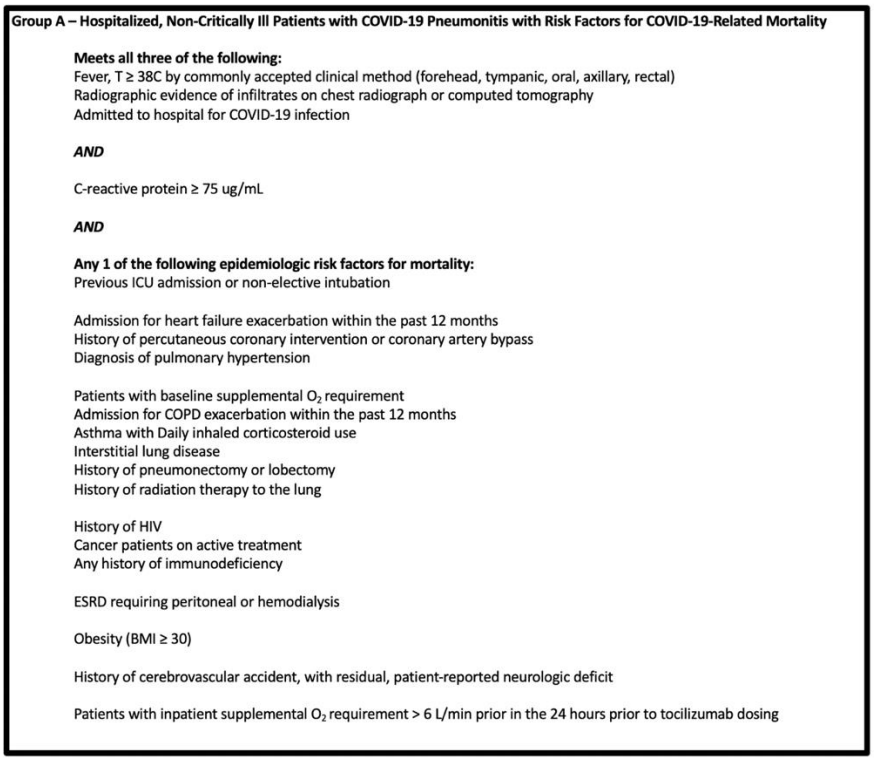

Figure 3. Group A. Clinical, laboratory, and epidemiologic characteristics of hospitalized, non-critically ill patients with COVID-19 pneumonitis at higher risk for clinical decompensation, ICU utilization, and COVID-19 disease-related mortality.

The crucial role of IL-6 in context of the risk of inhibiting innate antiviral response with these high doses of tocilizumab (400mg or 8mg/kg) is not insignificant.[41,42] We therefore believed that a) it was prudent to begin proactive treatment of these patients (which is expected to be confirmed with prospective RCT data[19]) and b) it was reasonable to use a tocilizumab dose that is lower than reported by others. We identified efficacious doses of 40mg and 120mg in COVIDOSE-1.

We have arrived at this dose through the initial COVIDOSE-1 study. The majority of patients in both Group A and Group B had clinical and biochemical response to the starting doses of 200mg and 80mg, respectively. Based on trial operating committee meeting and unanimous decision, the doses were decreased to 120mg and 40mg. With these lower doses, the majority of patients continued to have clinical and biochemical response.

Additionally, post-hoc analysis of recovery time yielded promising results: Time to recovery was calculated for enrolled COVIDOSE-1 patients who survived. Median time to recovery for the entire COVIDOSE-1 population was 3 days (interquartile range, 2-5). When stratified by COVIDOSE-1 risk group assignment, Group A patients had median time to recovery of 4.5 days (IQR, 2.5-6.75) while those in Group B had median time to recovery of 3 days (IQR, 2-4). In the first cross-trial comparison between tocilizumab and remdesivir, patients with a requirement for supplemental oxygen who received remdesivir had median time to recovery of 7 days (95% CI 6-8),[10] while this

subpopulation in COVIDOSE-1 had median time to recovery of 4 days (IQR, 3-5) despite the COVIDOSE-1 protocol selecting for patients with comorbidities. COVIDOSE-1 was a single-arm adaptive phase 2 study and recovery time was evaluated *post hoc*, thus there remains equipoise as to whether low-dose tocilizumab is clinically beneficial to patients with COVID-19 pneumonitis – this is the key question to be addressed by COVIDOSE-2.

1.2.7 **Early Termination of the COVIDOSE-1 Study**

During the course of the COVIDOSE-1 study, industry- and NIH-sponsored studies of remdesivir were being conducted worldwide.[10,43] The NIH-sponsored study reported, in press release form, that remdesivir use was associated with decreased hospital length of stay and "trended toward" improvement in survival (~30% decrease in the case-fatality rate).[10,44] Shortly thereafter, the Food and Drug Administration released an Emergency Use Authorization (EUA) letter for remdesivir, making it the antiviral standard of care in COVID-19.[45] Availability of the medication through the EUA, however, remains uncertain and further innovation is necessary.

The originally intended enrollment of COVIDOSE-1 was 50 patients. After the enrollment of the thirty-second COVIDOSE patient, however, remdesivir became generally available in the United States under the EUA. To that point, COVIDOSE-1 was successful in identifying a practical and pharmacodynamically effective low-dose of tocilizumab – 40 milligrams – that represents one-half of tocilizumab's smallest vial, making for convenient dosing and scalability. Rather than amend the COVIDOSE-1 protocol to continue enrollment and seek determination of the minimum effective dose of tocilizumab while simultaneously dealing with heterogeneous data to make pharmacodynamic inferences, we opted instead to close enrollment of COVIDOSE-1 and pivot toward the question of whether low-dose tocilizumab truly has efficacy in COVID-19 disease, particularly in combination with remdesivir.

COVIDOSE-1 identified no concerning safety signals, and there was preliminary evidence for both pharmacodynamic and clinical efficacy of low-dose tocilizumab. Even in the absence of full accrual, there is equipoise for a randomized, controlled trial. In terms of the recently published COVID-GRAM risk score,[46] Groups A and B appeared to have equivalent risks of decompensation, intensive care utilization, and COVID-19-related death. Participants in Group A had median (IQR) score of 126.8 (113.5, 151.8) while those in Group B had median (IQR) score of 125.2 (102.3, 158.9). These are not differences significant enough to justify risk-stratification on the basis of Group A and Group B in a randomized, controlled trial. Moreover, COVID-GRAM has not been prospectively validated, let alone used for risk stratification purposes in a randomized, controlled trial. Finally, it is not clear at this time that a higher dose of tocilizumab is needed for patients at higher risk – that is one of the questions being addressed by COVIDOSE-2.

1.3 Endpoints

1.3.1 The Need for Rapid Pharmacodynamic Endpoints

COVID-19 disease is a rapidly changing landscape with acute pressures on the US healthcare system and individual patients. In a rapidly evolving situation, the presence of new clinical data points including changes in vital signs and laboratory parameters are necessary to guide clinical decisions. By the same token, evaluation of the efficacy of provisioned medications is necessary so as to guide clinical and study management. In line with the natural history of COVID-19, we propose incorporation of 24-hour clinical and biochemical endpoints.

1.3.2 CRP is correlated with IL-6-axis signaling

Prior literature on serologic markers of inflammation in COVID-19 disease show markedly elevated levels of both CRP and IL-6.[17] Cytokines such as IL-6 are not universally available in clinical laboratories, however CRP tends to be.

Prior work from the immunology literature demonstrates a strong connection between CRP elevation and the presence of IL-6 signaling,[47] with IL-6-axis signaling serving as the predominant inducer of CRP expression.[48] In the rheumatoid arthritis disease state in which the IL-6 axis is not targeted with therapy, CRP and IL-6 are tightly correlated, as well. Though tocilizumab administration is typically followed by a *rise* in serum IL-6 levels (likely due to increased free IL-6 serum concentrations after blockade of the IL-6R by tocilizumab),[49] CRP declines, suggesting a decrease in effective IL-6 axis signaling. Within the context of COVID-19, IL-6 and CRP are correlated, as well.[50]

1.3.3 CRP and Fever Briskly Respond to Tocilizumab in COVID-19

Critically ill patients treated with tocilizumab 400mg experience rapid improvement in fever and CRP levels.[18,51] Based upon our independent evaluation of previously published data and an estimated CRP half-life of 19 hours,[18,52] we infer that approximately 85% of critically ill patients with COVID-19 treated with tocilizumab 400mg would experience either a CRP decline of $> 25\%$ or a normalization of CRP to < 10 μg/mL within 24 hours of dose administration.[37] Furthermore, *all* febrile patients with COVID-19 disease who were treated with tocilizumab 400mg experienced resolution of their fever within 24 hours of dose administration (reconstituted data are available upon request).[37] On the basis of these data and the absence of a dose-response relationship for tocilizumab in CAR-T-related CRS (1.2.4), *any* effective dose of tocilizumab should have clinical and biochemical effects similar to those of the 400mg dose.

This prediction was verified in the COVIDOSE-1 trial, where our preliminary data show that approximately 85% and 75% of patients experienced CRP and fever decline, respectively, after a single dose of tocilizumab, and only 15% of patients required re-dosing. In comparison, a COVIDOSE-1-eligible retrospective control population, derived from a de-identified clinical data warehouse, experienced CRP and fever decline in 34% and 14% of cases, respectively. In only 12.5% (4 of 32 cases) was there discordance between CRP decline and clinical outcome, suggesting the ability of COVIDOSE-1's inclusion and exclusion criteria to identify those patients likely to respond to therapy.

1.3.4 Justification for CRP Cutoffs

Evidence collected thus far in COVID-19 suggests C-reactive protein (CRP) as a useful proxy marker for serum IL-6 levels as well as COVID-19 disease-related inflammation in hospitalized patients, both critically ill and non-critically ill.[53-55] Early reports from the University of Chicago experience demonstrate that admission CRP is elevated in approximately 90% of hospitalized patients with COVID-19 disease (using an institutional normal range of < 5 μg/mL). Moreover, maximal AUROC for CRP from early studies of COVID-19 mortality is found at a CRP cutoff of 40 mg/L.[50]

Preliminary multivariate regression analysis of clinical and laboratory factors suggests CRP is correlated with COVID-19 related morality (unpublished data). Validation of these findings at our institution and others using either a test data set or prospective cohort study has not yet been completed. The goal of the overarching treatment strategy discussed in 1.2.4 is to provision potentially efficacious therapy to the greatest number of patients likely to benefit from tocilizumab while still preserving an adequate supply for critically ill patients.

1.3.5 Incorporation of Ordinal Clinical Endpoints

To date, the ideal clinical endpoints for COVID-19-related clinical trials remain unknown. Given the nature of this pandemic and the potential for health system collapse, therapeutic "success" and "failure" should account for individual patients' outcomes – clinical improvement and survival – as well as outcomes with *systems*-level implications – avoidance of mechanical ventilation, length of hospital stay, and avoidance of mechanical ventilation. Under normal circumstances, time to recovery for an individual highly likely to recover in the absence of a therapeutic intervention may not be all that important a clinical outcome – but these are not normal times. Marginal improvements in hospital length of stay and clinical improvement may serve the function of reducing hospital crowding, limiting nosocomial transmission, and providing something of a backstop for re-opening strategies.

Rather than target certain physiologic parameters in COVID-19, ordinal scales of clinical severity are the mainstay of COVID-19 clinical trials, imperfect though they may be. The ACTT study, an NIAID-sponsored double-blind, randomized, controlled trial of remdesivir in hospitalized patients with COVID-19 that thus far represents the gold standard in COVID-19 clinical trial design, incorporates an eight-point ordinal scale of disease severity ranging from not hospitalized and without limitation on activities (1) to death (8) in its secondary outcome measures, as defined by the *first assessment* on a given study date.[10] "Successes" included: 1) Improvement in one category using the ordinal scale (as indicated by the secondary outcome measure of 'time to improvement of one category') and 2) improvement by two categories using the ordinal scale (as indicated by the secondary outcome measure of 'time to improvement of two categories'). Time to recovery was defined as achieving one of the three statuses: "hospitalized without any requirement for medical care" (category 3), "not hospitalized with limitation on activities" (category 2), or "not hospitalized without limitation on activities" (category 1).[10]

In the Gilead-sponsored randomized, controlled trial of remdesivir, a seven-point ordinal scale was incorporated, ranging from death (1) to not hospitalized (7). Intermediate points on the scale were otherwise the same as in the ACTT trial. The primary outcome measure of this study was the odds ratio representing the odds of improvement in the ordinal scale on day 14.[43]

Large randomized, controlled trials of anti-IL6 axis therapies incorporate a similar ordinal framework. The aforementioned COVACTA study utilized the same seven-point ordinal scale, with an ill-defined primary outcome measure described as "clinical status". Derivative secondary outcome measures included time to clinical improvement, marked by National Early Warning Score of 2 or less, maintained for 48 hours and/or improvement of at least 2 categories relative to baseline when using the seven-point scale.[56]

The Sanofi/Regeneron-sponsored adaptive phase 2/3 trial of sarilumab in COVID-19 incorporates this same seven-point ordinal scale, with time to improvement being the outcme measure and *improvement* being defined as a *two-point* improvement in the ordinal scale.[20] Of note, the phase 3 portion of the sarilumab study will only proceed in a population of patients with critical COVID-19.[20]

The CORIMUNO-TOCI trial incorporates the eleven-point World Health Organization (WHO) scale of COVID-19 disease progression, ranging from uninfected (0) to death (10).[57] The WHO scale utilizes the physiologic parameter of P/F ratio (or SpO2/FiO2) as well as use of pressors to separate mechanically ventilated patients into three categories (categories 7-9). For the purposes of disease severity, CORIMUNO-TOCI split its population into two populations on the basis of severity: Group 1, with a WHO score of 5 or less, corresponding to nasal cannula supplemental oxygen requirement, and Group 2, with a WHO score of 6 or more, corresponding to non-invasive mechanical ventilation or high-flow nasal cannula.[57]

Finally, the forthcoming REMDACTA trial studying the combination of remdesivir and tocilizumab in patients with severe/critical COVID-19 will incorporate the 7-category ordinal scale utilized in Gilead-sponsored studies of remdesivir.

1.3.6 **Selection of an Ordinal Scale Relevant to Tocilizumab**

COVIDOSE-2's primary aim is to identify whether low-dose tocilizumab versus standard of care – which is expected to include remdesivir in the majority of patients – confers clinical benefit. Although not validated and developed empirically, the ordinal clinical scales used above are intuitive and can apply. The ordinal scale's use as a primary outcome measure in the above clinical trials of IL-6 axis-directed therapies limits the ambiguity of cross-trial comparisons. The ordinal scale's use as a primary outcome measure in studies of remdesivir may also aid in addressing the hypothesis that tocilizumab and remdesivir, by virtue of their different mechanisms of action, may be synergistic. Ordinal scales are appropriate for this study.

We have selected the same ordinal scale used in the Gilead remdesivir international trials, a seven-point ordinal scale: 1) Death; 2) Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, receiving non-invasive mechanical ventilation or high flow oxygen devices; 4) Hospitalized, requiring low-flow supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen or ongoing medical care (ed: used largely for infection control purposes); 7) Not hospitalized (ed: with or without limitation on activities and/or requiring home oxygen).

Adapting the definition of clinical recovery from ACTT, our primary outcome measure will be the time to recovery as defined by achievement of status 6 or 7 on the seven-point ordinal clinical scale of COVID-19 severity, in line with the definition of clinical recovery used in the ACTT trial of remdesivir.[10]

2 OBJECTIVES AND HYPOTHESES

2.1 Primary Objective and Hypothesis

Sub-Study A
Primary Objective A: To establish whether low-dose tocilizumab reduces the time to clinical recovery in patients with COVID-19 pneumonitis and hyperinflammation, when compared to a tocilizumab-free standard of care.

Hypothesis A: We hypothesize that low-dose tocilizumab, when compared to a tocilizumab-free standard of care, decreases the time to recovery in hospitalized, non-invasively ventilated patients with COVID-19 pneumonitis and hyperinflammation by three days or more.

Sub-Study B
Primary Objective B: To establish whether low-dose tocilizumab is near-equivalent to high-dose tocilizumab (400mg or 8 mg/kg) in reducing the time to clinical recovery in patients with COVID-19 pneumonitis and hyperinflammation.

Hypothesis B: We hypothesize that low-dose tocilizumab is near-equivalent to high-dose tocilizumab (400 mg or 8 mg/kg) in reducing the time to clinical recovery in hospitalized, non-invasively ventilated patients with COVID-19 pneumonitis and hyperinflammation.

2.2 Secondary Objectives and Hypotheses

Sub-Study A
Secondary Objective A1: To establish whether low-dose tocilizumab increases the probability of clinical recovery at seven days in COVID-19 pneumonitis.

Secondary Hypothesis A1: Low-dose tocilizumab increases the probability of clinical recovery at seven days in hospitalized, non-invasively ventilated patients with COVID-19 pneumonitis and hyperinflammation when compared to a tocilizumab-free standard of care.

Secondary Objective A2: To establish whether low-dose tocilizumab decreases signs, symptoms, and laboratory evidence of COVID-19 hyperinflammation.

Secondary Hypothesis A2: Low-dose tocilizumab increases the probability of fever resolution and CRP decline consistent with IL-6 signaling inhibition at 24 hours when compared to a tocilizumab-free standard of care.

Sub-Study B
Secondary Objective B1: To establish whether low-dose tocilizumab is nearly equivalent to high-dose tocilizumab in increasing the probability of clinical recovery at seven days in COVID-19 pneumonitis.

Secondary Hypothesis B1: Low-dose tocilizumab is nearly equivalent to high-dose tocilizumab in increasing the probability of clinical recovery at seven days in hospitalized, non-invasively ventilated patients with COVID-19 pneumonitis and hyperinflammation.

Secondary Objective B2: To establish whether low-dose tocilizumab is nearly equivalent to high-dose tocilizumab in decreasing signs, symptoms, and laboratory evidence of COVID-19 hyperinflammation.

Secondary Hypothesis B2: Low-dose tocilizumab is nearly equivalent to high-dose tocilizumab in increasing the probability of fever resolution and CRP decline consistent with IL-6 signaling inhibition at 24 hours.

3 SITE SELECTION

We intend to conduct this trial in collaboration with other medical centers within the United States, as well as internationally. We will amend the protocol to add outside sites as they are defined.

4 PATIENT SELECTION

4.1 Number of Subjects

We anticipate maximum enrollment of 332 total patients from various medical institutions during this adaptive clinical trial, distributed equally between the two sub-studies. Information published while the trial is being conducted may lead to a firmer definition of "standard of care". In this case, one of the two sub-studies will be prioritized and meet accrual target while the other may not.

4.2 Inclusion Criteria

- Adults ≥ 18 years of age
- Approval from the patient's primary inpatient service

- Hospitalized
- Positive test for active SARS-CoV-2 infection
- Radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT)
- Ability to provide written informed consent on the part of the subject or, in the absence of decisional capacity of the subject, an appropriate surrogate (e.g. a legally authorized representative).
- CRP ≥ 40mg/L

4.3 **Exclusion Criteria**

- Concurrent use of invasive mechanical ventilation or helmet ventilation
- Concurrent use of vasopressor or inotropic medications
- Concurrent receipt of convalescent plasma therapy or in the 30 days preceding enrollment
- Previous receipt of tocilizumab or another anti-IL6R or IL-6 inhibitor in the year prior.
- Known history of hypersensitivity to tocilizumab.
- Diagnosis of end-stage liver disease or listed for liver transplant.
- Elevation of AST or ALT in excess of 10 times the upper limit of normal.
- Neutropenia (Absolute neutrophil count < 500/uL).
- Thrombocytopenia (Platelets < 50,000/uL).
- On active therapy with a Bruton's tyrosine kinase-targeted agent, which include the following:
    - Acalabrutinib
    - Ibrutinib
    - Zanubrutinib

- On active therapy with a JAK2-targeted agent, which include the following:
    - Tofacitinib
    - Baricitinib
    - Upadacitinib
    - Ruxolitinib

- Any of the following biologic immunosuppressive agent (and any biosimilar versions thereof) administered in the past 6 months or less::
    - Abatacept
    - Adalimumab
    - Alemtuzumab
    - Atezolizumab
    - Belimumab
    - Blinatumomab
    - Brentuximab
    - Certolizumab

- Daratumumab
- Durvalumab
- Eculizumab
- Elotuzumab
- Etanercept
- Gemtuzumab
- Golimumab
- Ibritumomab
- Infliximab
- Inotuzumab
- Ipilimumab
- Ixekizumab
- Moxetumomab
- Nivolumab
- Obinutuzumab
- Ocrelizumab
- Ofatumumab
- Pembrolizumab
- Polatuzumab
- Rituximab
- Rituximab
- Sarilumab
- Secukinumab
- Tocilizumab
- Tositumumab
- Tremelimumab
- Urelumab
- Ustekinumab

- History of bone marrow transplantation (including chimeric antigen receptor T-cell) or solid organ transplant
- Known history of Hepatitis B or Hepatitis C (patients who have completed curative-intent anti-HCV treatments are not excluded from trial)
- Positive result on hepatitis B or C screening
- Known history of mycobacterium tuberculosis infection at risk for reactivation
- Known history of gastrointestinal perforation
- Known history of or active diverticulitis
- Multi-organ failure as determined by primary treating physicians
- Any other documented serious, active infection besides COVID-19 – including but not limited to: lobar pneumonia consistent with bacterial infection, bacteremia, culture-negative endocarditis, or current mycobacterial infection – at the discretion of primary treating physicians
- Pregnant patients or nursing mothers

- CRP < 40 mg/L

4.4 Gender, Age, Racial and Ethnic Origin of Subjects

Men and women of all races and ethnic groups are eligible for this trial.

5 REGISTRATION AND DATA COLLECTION/MANAGEMENT

5.1 General Guidelines

Patients will be identified as potential participants in this clinical trial by *in silico* screening of patients via electronic medical records (EMRs) when available. Primary teams and emergency department teams are encouraged to securely send medical record numbers of potentially eligible patients to study investigators at their respective institutions. When EMR not available, we recommend primary inpatient treating health care teams or emergency department teams make the study investigators aware of eligible patients.

Prior to approaching the patient for recruitment, we will approach the patient's treating team for permission and to discuss the standard of care (SOC) treatment plan as well as the study design. As indicated in the study schematic on page 4, the study consists two sub-studies that each include 3 arms.

Sub-study A:
- SOC (routine treatment plan includes no tocilizumab)
- Tocilizumab 40mg
- Tocilizumab 120mg

Sub-study B:
- SOC (routine treatment plan includes tocilizumab 400mg or 8mg/kg)
- Tocilizumab 40mg
- Tocilizumab 120mg

Sub-study assignment for each subject is done in collaboration with the patient's treating physican team. The treating team will be given the option to choose which sub-study might be most appropriate for their patient based on their intended treatment plan. For example, if the team did not intend to use tocilizumab as part of their treatment plan, they would likely choose Sub-study A. However, if the intended treatment plan was to include tocilizumab (at the emerging Covid-19 standard of care doses of 400mg or 8mg/kg), then they would likely choose sub-study B. Once the sub study has been assigned, randomization occurs (1:1:1) within the respective sub study.

Before any study-specific evaluations are performed, all patients must have given informed consent for the study. Patients must meet all of the eligibility requirements listed in Section 3.0. Eligible patients will be entered into the University of Chicago's REDCap database used for both registration and data collection.[58] An investigator will confirm eligibility criteria and the informed consent process and a member of the study team will complete the registration case report form.

(1) Patient screened: by investigators electronically via EMR or after primary inpatient or emergency department teams make investigators aware of patient eligibility
(2) Sub-study designation: Study investigators confirm with primary team the decision regarding appropriate sub-study for patient.
(3) Reciept of Informed consent: Informed consent from patient received and confirmed
(4) Randomization: Pre-designated study investigator(s) will perform the randomization within the aforementioned sub-study to determine which dose of tocilizumab (if any) patient will receive – and relay this information to primary clinical team in real time (as to avoid delay of drug administration).
(5) Recording in REDCap: Patient eligibility and patient information recorded into REDCap database through the use of online REDCap report

5.2 Informed Consent Process

Given the unique nature of the COVID-19 pandemic and the risk for transmission to health care and research staff, we will obtain informed consent from possible participants by the following process, using exclusively electronic means to obtain consent:

Electronic consent:

1. Screening via electronic medical records and/or collaboration via primary clinical team regarding patient eligibility
2. Study investigators confirm with primary team the sub-study designation the primary team feels appropriate for patient
3. Patient called by study investigators to determine if patient willing to discuss research opportunity and willing to receive consent via email. If the patient does not have access to email at the time, a paper form can be delivered directly to the subject.
4. Discussion between study investigators and patient while reading through consent.
5. If patient agrees and willing to participate, the subject will be asked to verify identity by providing their date of birth, and last four digits of social, which will be verified against records in Epic. We will then obtain written consent via electronic signature through RedCAP.

Paper Consent:
If consent signature through RedCAP is not possible, a written consent via signed paper copy will be obtained, using safe practices as determined by individual institutional policies.

Proxy Consent
Electronic Consent:

In the event of the patient's inability to provide informed consent for the study, an appropriate surrogate decision-maker (e.g., next of kin or legally authorized representative) may make the consent decision on the patient's behalf. This will be performed in the following manner:

1. Screening via electronic medical records and/or collaboration via primary clinical team regarding patient eligibility
2. Study investigators confirm with primary team the sub-study designation the primary team feels appropriate for patient
3. Clarification of patient's consentability.
4. If patient cannot be consented, patient's surrogate decision-maker is called by study investigators to discuss further.
5. On video call, surrogate decision-maker will verify his/hers/their identity by showing ID during video conference (surrogate physically shows their ID card/license)
6. Once surrogate decision-maker identity verified, study investigator will discuss surrogate decision-maker's willingness to to discuss research opportunity and receive consent via email.
7. Surrogate decision-maker sent email with consent form, with appropriate copying of the patient if email is available.
8. Discussion between study investigators and surrogate decision-maker while reading through consent.
9. If surrogate decision-maker agrees and is willing to provide informed consent for the patient on his/her behalf, we will obtain written consent via electronic signature through RedCAP.

Paper Consent:
If consent signature through RedCAP is not possible, a written consent via signed paper copy will be obtained either in person or via traditional mail. A conversation will take place between a member of the study team and the subject's surrogate, explaining the study and answering any questions (either in person, over the phone or over video call) before signing the consent form. The proxy will be provided with a final signed copy of the consent (if traditional mail is used, the proxy will mail the signed copy of the consent to the study team, who will sign and mail a copy back to the proxy).

5.3 Exemption from Investigational New Drug Application

Investigational New Drug (IND) is not required at this time, on the basis of September 2013 Food and Drug Administration Guidance [59], section IV.A. This study meets all conditions set forth:

- It studies a drug product, tocilizumab, legally marketed in the United States.
- The intent of the study is *not* to report to FDA a well-controlled study in support of label change.
- The intent of the study is *not* to support a change in marketing practices.

- This study focuses on the COVID-19 patient population who have been admitted to the hospital. The mortality for COVID-19 among inpatients is quoted as greater than 25% [8]. Though it is a new clinical situation in which to study tocilizumab, it is *not* prohibitively high-risk. Moreover, it does not represent a prohibitively large increase in risk over the baseline risk faced by this unique and ill patient population. Despite the presence of the global COVID-19 pandemic, tocilizumab continues to be administered at doses nearly an order of magnitude higher than the doses proposed in this study to patients with rheumatologic conditions such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis. If the risk/benefit calculus of the practice of continuing high-dose tocilizumab is acceptable at this time, then this study, with its comparable risk/benefit calculus, is as well. Furthermore, an emerging standard of care in critical COVID-19 disease is the use of tocilizumab at a dose significantly higher than the doses under study.
- The study will be reviewed and conducted under the jurisdiction of an Institutional Review Board in accordance with 21 CFR part 56 and will have informed consent as described below, in accordance with 21 CFR part 50.
- The study is *not* intended to promote or commercialize tocilizumab.

Tocilizumab is currently used off-label around the world for management of COVID-19 pneumonitis, including domestically, in Europe, and in Asia. At present time, however, there is no level 1 evidence of tocilizumab's benefit on either time to clinical recovery or overall mortality in COVID-19 pneumonitis. It is possible that randomized controlled trial evidence reported in the near future will show that tocilizumab is better than no additional drug therapy.

The response of investigators to new tocilizumab-related evidence and government action should be proportional to the strength of evidence. In the event of EMA or FDA approval of tocilizumab for the treatment of COVID-19 pneumonitis, study investigators would suspend enrollment and amend the trial protocol. Note that Emergency Use Authorization (EUA) definitionally does not require the same level of evidence and/or quality control as a normal, "peacetime" FDA approval. As such, there remains ambiguity as to whether the drug is truly beneficial even following EUA. Given this ambiguity, therefore, the presence of an EUA for tocilizumab will not lead to trial suspension and protocol amendment.

5.4 Registration Process

To complete the registration process, a member of the study team will:

1.) Confirm with treating physicians the assignment for sub-study (A or B) the treating clinical team feels appropriate for patient. This will essentially designate whether the patient receives no tocilizumab (sub-study A) or high-dose tocilizumab (sub-study B) if randomized to the standard of care arm.
2.) Assign the patient a study number coded to the study site and sub-study (e.g. first University of Chicago patient on sub-study A would be UC-A-001)
3.) Register the patient on the study (and relevant sub-study)

4.) Randomize the patient to low-dose tocilizumab 40mg, low-dose tocilizumab 120mg, or standard of care arm.
5.) Record the values of pre-treatment laboratory studies as below.

When registering a subject, the following must occur:

- The patient must have signed the consent form (or his/her proxy/surrogate/legally authorized representative will have completed the electronic consent form via REDCap) or evidence of a signed paper consent.
- The date the patient is registered will be considered the patient's "On Study Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by REDCap on this date.

The University of Chicago will maintain the secure, password protected, and regularly backed up REDCap clinical trials database. All data will be entered into the REDCap database. Collaborating institutions will complete daily summaries for the trial using the RedCAP secure web survey interface, thereby ascribing the same level of data protection and convenience to trial form completion that will be used in the consent process. Data will be stored in RedCap using the patient-study number.

5.5 **Randomization and Stratification**

The patient's primary treating team will determine which of the two sub-studies in which to enroll the patient, Sub-study A or Sub-study B. Following the determination of sub-study assignment, all patients will be randomized to one of three respective arms in 1:1:1 ratio.

Sub study A:

- SOC (routine treatment plan includes no toci)
- Tocilizumab 40mg
- Tocilizumab 120mg

Sub study B:

- SOC (routine treatment plan includes toci 400mg or 8mg/kg)
- Tocilizumab 40mg
- Tocilizumab 120mg

Randomizations will be generated by the study statistician using the method of permuted blocks, stratified by 1) the presence or absence of expanded use access (EUA) remdesivir *and* 2) the presence or absence of systemic corticosteroid administration (at a dose higher than the patient's pre-hospitalization baseline steroid use) in order to achieve overall balance between the arms in terms of their exposures to presumed efficacious antivirals and baseline, pre-treatment severity. Randomization will be implemented using the randomization module present in the REDCap software suite and readily available to study investigators who are participating in the consenting process.

Patients will remain on their allocated arm for the study's duration. Clinical decompensation to the point of requiring additional use of IV tocilizumab or any other anti-inflammatory monoclonal antibody (e.g., siltuximab, anakinra, sarilumab) by

primary team for therapy of hyperinflammation secondary to COVID-19 will qualify as a failure.

Patients and their primary teams will be notified by investigators of the patient's randomized group assignment within 2 hours of randomization, with the patient receiving his/her baseline CRP laboratory draw and tocilizumab dose (if applicable) on the same calendar day. Delays in treatment initiation – for example, due to a patient no longer being eligible for study or withdrawing consent – should be discussed with the Principal Investigator.

5.6 **Data to Collect**

The following baseline clinical variables will be collected and recorded on the Eligibility and Registration Form:

- Sub-study assignment
- Age
- Sex
- Race and Ethnicity, self-identified
- COVID-19-related medications (including antiviral, anti-inflammatory, and immunomodulatory drugs)
- Complete medication list (pre-hospitalization and during hospitalization)
- Complete medical history, with particular attention to the following medical comorbidities:
    - Previous ICU admission
    - Previous non-elective intubation
    - Admission for heart failure exacerbation within the past 12 months
    - History of percutaneous coronary intervention (PCI)
    - History of coronary artery bypass graft (CABG) surgery
    - History of cerebrovascular accident with residual, patient-reported neurologic deficit
    - Diagnosis of pulmonary hypertension
    - Prior to admission requirement for supplemental O_2
    - Diagnosis of interstitial lung disease (ILD)
    - Admission for chronic obstructive pulmonary disease (COPD) exacerbation within the past 12 months
    - Asthma with use of daily inhaled corticosteroid
    - History of pneumonectomy or lobectomy
    - History of radiation therapy to the lung
    - History of HIV
    - Cancer of any stage and receiving active treatment (excluding hormonal therapy)
    - Any history of diagnosed immunodeficiency
    - End-stage renal disease (ESRD) requiring peritoneal or hemodialysis
    - BMI >30 kg/m^2
    - Baseline supplemental oxygen required (in 24hrs prior to first tocilizumab dose) >6L/min Nasal cannula

The following laboratory data are **required** to be collected within 24 hours prior to tocilizumab administration will be reviewed and tracked by investigators. The following data are required for eligibility, safety and clinical management purposes:

- White blood cell count
- Absolute lymphocyte count (ALC)
- Absolute neutrophil count (ANC)
- Hemoglobin
- Platelets
- AST (SGOT)
- ALT (SGPT)
- BUN
- Creatinine

The following laboratory data are **recommended** to be collected within 24 hours prior to tocilizumab administration will be reviewed and tracked by investigators. The following data are recommended for clinical management purposes and secondary analysis:

- D-dimer
- Fibrinogen
- Lactic dehydrogenase (LDH)
- Westergren sedimentation rate (ESR)
- Ferritin
- IL-6
- Triglycerides
- High-sensitivity troponin

The following laboratory data is **required** to be collected within 12 hours prior to tocilizumab administration to determine eligibility and will be reviewed and tracked by investigators:

- C-reactive protein (CRP)

In addition, all patients are **required** to have the following baseline laboratory data collected in the 2 hours prior to administration of tocilizumab. It will be used for assessment of pharmacodynamic response and may be used for clinical management:

- CRP

For the first post-tocilizumab follow-up, investigators **require** the following laboratory be performed at 27 +/- 3 hours following tocilizumab administration for assessment of pharmacodynamic response and may be used for clinical management:

- CRP

Investigators **strongly recommend** the following laboratory study to be collected at 24-hour intervals during the patient's hospitalization (or with clinical decompensation) for the purposes of **clinical management, safety, and consequently adverse event reporting**:

- White blood cell count

- Absolute lymphocyte count (ALC)
- Absolute neutrophil count (ANC)
- Hemoglobin
- Platelets
- AST (SGOT)
- ALT (SGPT)
- BUN
- Creatinine

Regarding these aforementioned labs: no labs will be drawn solely for research purposes if not available through clinical care (even if denoted as "required").

Optional Sample
For the purposes of secondary analysis and identification of predictors of tocilizumab response, University of Chicago Medicine patients will have the option (as a separate line item in the consent document) to allow investigators to use leftovers from tubes of blood drawn for clinical tests that would otherwise be discarded. This will apply to any blood collected during that respective hospital stay as well as up to 1 year after study enrollment. The following correlates will be analyzed:

- Cytokine analysis
- Measurement of anti-SARS-CoV-2 antibodies

All labs and tocilizumab doses while inpatient will be collected on the Labs and Tocilizumab Administration Form, which will be made available to collaborating institutions in the RedCAP web interface. If the patient has a change in clinical status requiring the use of invasive mechanical ventilation, initiation of vasopressor support, or (for patients *not* requiring non-invasive mechanical ventilation upon admission) the use of non-invasive mechanical ventilation, please record labs on the Patient Change in Clinical Status Labs Form, which will be made available to collaborating institutions in the RedCAP web interface. If the patient subsequently improves and no longer requires the critical care parameter(s), please complete a second Patient Change in Clinical Status Labs Form, which will be made available to collaborating institutions in the RedCAP web interface. For every dose of tocilizumab administered, please record the details (dose amount, date, time, etc.) on the Labs and Tocilizumab Administration Form, which will be made available to collaborating institutions in the RedCAP web interface.

When a patient is in follow-up, they will be followed for survival for 28 days following the first dose of tocilizumab or hospital discharge, whichever occurs latest. The details will be recorded on the Follow-Up Form, which will be made available to collaborating institutions in the RedCAP web interface.

On a daily basis the clinical status of the patient will be assessed by CRC/clinicians. Based on the assessment and documentation of the clinical team of record caring for the patient, the ordinal score will be assigned by study team. Key phrases to distinguish between a category 5 patient ("Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or otherwise)") – and a category 6

patient ("Hospitalized, not requiring supplemental oxygen or ongoing medical care") would include the following (or approximate versions thereof): "Awaiting disposition", "pending placement", "awaiting transport", "awaiting negative test for placement", or "requires negative test for dialysis center". Any patients who do not meet these would need to be adjudicated by DMC in order to be made category 6. Patients who are hospitalized will be assumed to be category 5 unless proven otherwise.

5.7 Data Submission

All forms collected for the trial will be entered into the REDCap database.

6 DRUG ADMINISTRATION

Treatment will be administered to the patient on the day of their enrollment and while they are admitted. Tocilizumab is commercially available and will not be provided by the study.

In sub-study A, therapy will consist of tocilizumab administered at doses of 40mg (low-dose tocilizumab arm 1) or120mg (low-dose tocilizumab arm 2), or no tocilizumab at all. In sub-study B, therapy will consist of tocilizumab administered at doses of 40mg (low-dose tocilizumab arm 1), 120mg (low-dose tocilizumab arm 2), or 400 mg will be utilized, as discussed in sections 4.1 and 4.5.

6.1 Duration of Study

Therapy with a one-time dose of tocilizumab will proceed unless one of the following events occurs:

1. Treating physician determination prior to dose administration that the risks or downsides of tocilizumab administration outweigh the potential benefits.
2. Patient withdraws consent prior to dose administration
3. Patient is withdrawn from the study prior to dose administration at the discretion of the investigator or the patient's attending physician.

Patients will be followed for overall survival for 28 days after tocilizumab administration or liberation from mechanical ventilation, whichever occurs latest.

6.2 Amount of Treatment

Patients will receive only one on-protocol dose of tocilizumab. Patients will not be re-dosed as part of the trial protocol regardless of whether they have improvement in their biochemical and/or clinical parameters. If randomized to either of the low-dose tocilizumab arms of the study, the patient remains eligible to receive high-dose tocilizumab (400mg or 8mg/kg) at the discretion of primary treating physicians.

7 STUDY ASSESSMENTS

7.1 Pretreatment Evaluation

The following laboratory data are **required** to be collected within 24 hours prior to tocilizumab administration will be reviewed and tracked by investigators. The following data are required for eligibility, safety and clinical management purposes:

- White blood cell count
- Absolute lymphocyte count (ALC)
- Absolute neutrophil count (ANC)
- Hemoglobin
- Platelets
- AST (SGOT)
- ALT (SGPT)
- Blood urea nitrogen
- Creatinine
- Chest radiograph (CXR) (portable single-view is acceptable) or computed tomography (CT) of chest

The following laboratory data are **recommended** to be collected within 24 hours prior to tocilizumab administration will be reviewed and tracked by investigators. The following data are recommended for clinical management and secondary analysis purposes:

- D-dimer
- Fibrinogen
- Lactic dehydrogenase (LDH)
- Westergren sedimentation rate (ESR)
- Ferritin
- IL-6
- Triglycerides
- High-sensitivity troponin

The following laboratory data is **required** to be collected within 12 hours prior to tocilizumab administration to determine eligibility and will be reviewed and tracked by investigators:

- C-reactive protein (CRP)

The patient's score on the seven-point ordinal clinical scale (described in section 1.3.6) is **required** at the following timepoints:

- Study enrollment
- Randomization

7.2 On-Study Evaluation

On-study evaluation refers to measurement of vital signs and laboratory studies before and after a patient has received tocilizumab. Subjects will be monitored during and following the drug infusion to monitor for any complications or reactions. As part of routine care, subjects will be seen daily while in the hospital and will be monitored

through blood tests for general health as well as liver function. Vital signs will be monitored daily while in the hospital, physical exams, assessment of COVID-19, and CT scans or chest x-rays as necessary for routine care.

Patients will have the following laboratory study is **required** to be collected in the 2 hours prior to administration of tocilizumab and this value will be deemed the pre-tocilizumab or baseline value. It will be used for assessment of pharmacodynamic response and may be used for clinical management:

- CRP

For the first post-tocilizumab follow-up, investigators **require** the following laboratory be performed at 27 +/- 3 hours following tocilizumab administration for assessment of pharmacodynamic response and may be used for clinical management:

- CRP

The patient's score on the seven-point ordinal clinical scale (described in section 1.3.6) is **required** at the following timepoints:

- Tocilizumab administration (if applicable)
- Daily during patient's hospitalization
- 28 days following randomization and tocilizumab administration

In line with standard of care clinical management of COVID-19 patients, investigators **strongly recommend** the following laboratory study to be collected at 24-hour intervals during the patient's hospitalization (or with clinical decompensation) for the purposes of **clinical management, safety, and consequently adverse event reporting**:

- White blood cell count
- Absolute lymphocyte count (ALC)
- Absolute neutrophil count (ANC)
- Hemoglobin
- Platelets
- AST (SGOT)
- ALT (SGPT)
- BUN
- Creatinine

For the purposes of secondary analysis and identification of predictors of tocilizumab response, University of Chicago Medicine patients will have the option (as a separate line item in the consent document) to allow investigators to use leftovers from tubes of blood drawn for clinical tests that would otherwise be discarded. This will apply to any blood collected during that respective hospital stay as well as up to 1 year after study enrollment. The following correlates will be analyzed:

- Cytokine analysis
- Measurement of anti-SARS-CoV-2 antibodies

Collection and Handling of Specimens:
Clinical labs will be drawn and processed normally as per standard of care. No additional labs will be drawn solely for research purposes if not collected as part of clinical care.

Labs collected for secondary analysis will be stored in the University of Chicago Human Immune Monitoring Core Facility. Samples will be labeled with a unique study patient identifier, which will be linked to the patient's identifying information in a secure RedCap database. Barcodes reflecting the unique study patient identifier may be used on some blood samples to automate sample processing. There will not be any other identifying PHI on the stored samples. Blood samples will be stored at or below –80°C. After the study has been completed, samples will be de-identified and the linkage between the unique patient study ID and the patient's identifying information on RedCap will be removed. De-identified study samples may be stored indefinitely.

7.3 Off Study Assessments

Enrolled patients will be followed throughout their hospital course, and for survival for 28 days after receiving the first dose of tocilizumab.

7.4 Study Calendar

7.4.1 Overall Study Calendar

	Eligibility Assessment	Consent and Study Enrollment	Randomization	Pre-Tocilizumab Assessment	Post-Tocilizumab Assessment, 27 +/- 3 hours	Daily assessment after randomization, while hospitalized	Patient Intubated **OR** Patient transferred to ICU **OR** Patient change in clinical status	Patient Extubated **OR** Patient transferred from ICU	28 Days following tocilizumab
Written Informed Consent		X (require)							
Lab set 1[a]	X (require)				X (recommend)	X (recommend)	X (recommend)	X (recommend)	
Lab set 2[b]	X (require)			X (require)	X (require)	X (recommend)	X (recommend)	X (recommend)	
Lab set 3[c]		X (recommend)			X (recommend)		X (recommend)	X (recommend)	
Imaging[d]	X (require)						X (recommend)	X (recommend)	
Clinical Ordinal Status Assessment[e]	X (require)	X (require)	X (require)	X (require)	X (require)	X (require)	X (require)	X (require)	X (require)
Eligibility Confirmation	X (require)	X (require)	X (require)	X (require)					

[a] Set 1: WBC, ALC, ANC, hemoglobin, platelets, AST, ALT, BUN, Creatinine.
[b] Set 2: CRP.
[c] Set 3: D-dimer, fibrinogen, LDH, ESR, ferritin, IL-6, triglycerides, high-sensitivity troponin.
[d] For baseline assessment, imaging study should be completed within 48 hours of initial tocilizumab administration.
[e] Seven-point ordinal clinical scale as described in section 1.3.6. For each calendar day that the patient is enrolled on study, the patient's **worst** ordinal clinical status should be recorded and submitted along with all relevant study records.
[a, b, c, d] No imaging or labs will be conducted solely for research purposes if not conducted as part of clinical care.

8 SAFETY

8.1 Risks

Tocilizumab is a commercially available drug approved for the treatment of diseases other than COVID-19. To date, there is no prospective, randomized controlled trial data suggesting tocilizumab's efficacy in COVID-19. There is no standard dose of tocilizumab for COVID-19. The FDA-labeled dose of tocilizumab for CRS is 8 mg/kg. In comparing this dose to a reduced dose, there is a risk that the administration of reduced dose may be associated with poorer clinical outcomes for patients. Patients will be informed of this possibility.

Side effects and theoretical risks associated with tocilizumab include:

- Serious infections, including but not limited to:
    - Opportunistic infections such as tuberculosis, Cryptococcus, aspergillosis, candidiasis, and pneumocystis
    - Secondary bacterial infection such as ventilator-associated pneumonia (if later requiring mechanical ventilation), hospital-acquired pneumonia, bloodstream infection, urinary tract infection, cellulitis, herpes zoster, gastrointestinal infection, diverticulitis, septic arthritis
- Gastrointestinal perforation
- Hypersensitivity reaction, including anaphylaxis and death
- Neutropenia
- Thrombocytopenia
- Elevated liver enzymes
- Elevated lipids
- Immunogenicity (development of antibodies against tocilizumab)
- Hepatitis B virus reactivation
- Rarely, nervous system problems such as multiple sclerosis
- Tocilizumab may increase your risk of cancer
- Tocilizumab may harm unborn or nursing babies

Theoretical risks associated with tocilizumab in the context of COVID-19 infection include:

- Suppression of the adaptive antiviral immune system, resulting in progression of COVID-19

9 MEASUREMENT OF EFFECT

9.1 Time to Recovery

Day of recovery is defined as the first day on which the patient achieves one of the following two categories from the seven-point ordinal scale: 6) Hospitalized, not requiring supplemental oxygen or ongoing medical care or 7) Not hospitalized. Time to recovery is the number of days from randomization to achievement of this status. Note that the ordinal scale is measured once daily, with the patient's worst clinical status during the 24-hour time period (0:00-23:59) being documented.

9.2 Achievement of Recovery, 7 days

This will be defined as the percentage of patients in a given arm of the study achieving one of the above two categories on the ordinal scale on day 7 after randomization. Note that the ordinal scale is measured once daily, with the patient's worst clinical status during the 24-hour time period (0:00-23:59) being documented.

9.3 Overall Survival, 28 days

This will be defined as the percentage of patients in a given arm of the study who are alive 28 days following randomization. Patients who are discharged to hospice will be counted as deceased on the day of discharge. Patients who are transitioned to inpatient hospice or inpatient comfort measures only will be counted as deceased on the day of transition.

9.4 Hospital LOS

This will be defined as the number of days that pass between the day of a patient's randomization and his or her discharge from the hospital.

9.5 Clinical Response – Rate of Non-Elective Invasive Mechanical Ventilation (RNEIMV)

This will be a binary outcome defined as worsening COVID-19 disease resulting in the use of non-elective invasive mechanical ventilation during the course of the patient's COVID-19 infection.

9.6 Clinical Response – Duration of Non-Elective Invasive Mechanical ventilation (DNEIMV)

This will be a continuous outcome defined by the amount of time between initiation and cessation of non-elective non-elective invasive mechanical ventilation.

9.7 Clinical Response – Time to Non-Elective Invasive Mechanical ventilation (TNEIMV)

This will be a continuous outcome defined by the amount of time between randomization and the initiation of non-elective invasive mechanical ventilation. This will be treated as a time-to-event with possible censoring.

9.8 Clinical Response – Rate of Vasopressor/Inotrope Utilization (RVIU)

This will be a binary outcome defined as utilization of any vasopressor or inotropic medication.

9.9 Clinical Response – Duration of Vasopressor/Inotrope Utilization (DVIU)

This will be a continuous outcome defined by the amount of time between initiation of first and cessation of last vasopressor medications.

9.10 Clinical Response – Time to Vasopressor/Inotrope Utilization (TVIU)

This will be a continuous outcome defined by the amount of time between randomization and the initiation of any vasopressor or inotropic medication. This will be treated as a time-to-event with possible censoring.

9.11 Clinical Response – Duration of Increased Supplemental Oxygen from Baseline

This will be an ordinal outcome defined by the number of days counted from randomization over which the participant requires supplemental oxygen in excess over his/her baseline supplemental oxygen requirement. The supplemental oxygen requirement is defined as the highest liters-per-minute flow of supplemental oxygen required by the patient each day over the course of the hospitalization.

9.12 Biochemical Response - C-reactive Protein Response Rate

This will be a binary outcome defined as the presence or absence of a decline in CRP of ≥ 25% from baseline CRP in the 27 +/- 3 hours after tocilizumab administration, as compared to pre-treatment baseline.

9.13 Safety – Rate of Secondary Infection

This will be defined as the percentage of patients in a study arm who develop serious non-COVID-19 viral, bacterial, or fungal infections (e.g., bloodstream infection, hospital-acquired pneumonia, ventilator-associated pneumonia, opportunistic infection) following randomization and up to the 28-day assessment of overall survival.

10 STATISTICAL PLAN AND CONSIDERATIONS (10)

10.1 Sample Size Determination

The primary endpoint is time to recovery (TTR) as defined in section 8.1 above. Each subject will be followed for a minimum of 28 days. As in the ACTT-1 analysis,[10] patients who die or are discharged to hospice will be censored as of day 28 (or the longest follow-up time if >28 days). As a result patients censored on day >28 will reflect both any who did not recover as well as those who died. Kaplan-Meier curves will be generated and compared between the treatment arms using a logrank test stratified by remdesivir use and clinical status at enrollment as determined on the seven-point clinical ordinal scale.[60] Separate analyses will be performed for the two sub-studies, i.e., those whose standard of care includes no tocilizumab (superiority study) and those whose standard of care includes 400mg or 8mg/kg tocilizumab (near-equivalence study).

For the superiority study, patients will be randomized in a 1:1:1 ratio to 0mg, 40mg, or 120mg tociluzmab. The initial analysis will pool the 40mg and 120mg dose groups and contrast their TTR with the control arm (0mg). Sample size calculations are based on the results of the ACTT-1 trial. We assume that in our study population 25%, 65%, and 10% will fall into the risk strata depicted in Figures 2B, 2C, and 2D of the published results, corresponding to, respectively, patients not receiving supplemental oxygen at enrollment, patient receiving low-flow supplemental oxygen at enrollment, and patients receiving high-flow oxygen or noninvasive mechanical ventilation at enrollment.[10] The median

TTRs in the corresponding placebo and remdesivir groups were 6 vs. 5 days, 9 vs. 7 days, and 22 vs. 16 days, respectively. Assuming the distributions are roughly symmetrical, this implies a median/mean TTR for the non-remdesivir-treated, control arm patients in our study of 0.25(6)+0.65(9)+0.10(22)=9.6 days. For the remdesivir-treated subgroup, the median/mean will be assumed to be 0.25(5)+0.65(7) +0.10(16)=7.4 days. Finally, we predict 85% of our population will receive remdesivir and 15% will not, giving an overall median/mean TTR in the control arm of 0.85(7.4)+0.15(9.6)=7.7 days. Since patients will be assessed daily, we will assume a median control TTR of 8 days. In order to have 80% power to detect a reduction in the median TTR of 3 days with 40/120mg tocilizumab (rate ratio for recovery of 1.60), a sample size of 132 patients is required (44 per arm), based on a one-sided test at the alpha=0.05 signficance level.

In the near-equivalence study, patients will be randomized in a 1:1:1 ratio to 40mg, 120mg, or higher-dose (400mg or 8mg/kg) tocilizumab. Here the same sample size of 132 patients will provide 80% power to determine whether the true TTR under the 400mg dose is 3 days less than that for the pooled 40/120mg arms. It is recognized that our sample size will not be sufficient to formally establish non-inferiority of the lower doses—this would entail a much larger study. Thus the secondary endpoints—in particular, rate of secondary infection and toxicity as well as CRP as an efficacy biomarker—will also have an important role. As noted by Tannock *et al*, "there is usually minimal consideration of other measures of benefit due to ALT, such as reduced drug exposure and toxicity, or reduced cost leading to greater access. Non-inferiority trials can *'fail',* because the sample size is too small to provide the pre-specified level of statistical confidence for non-inferiority, even if the best estimates of efficacy of ALT and new-SOC are similar."[61] (Here "ALT" would correspond to the lower dose levels and "new-SOC" to the 400mg dose.) Thus the totality of evidence, including the estimated difference in TTR afforded by the higher dose together with its 95% confidence interval, the effects on secondary endpoints, toxicity, and the reduced cost and wider accessibility of the lower dose levels will be considered in the interpretation of the results.

10.2 **Definition of Evaluable Patients**

Patients are considered eligible for analysis if they have enrolled in the study and been randomized.

10.3 **Statistical Methods**

Time to recovery (TTR) will be estimated by the Kaplan-Meier method and compared between groups using a stratified logrank test.[60] As noted above, patients who die or transferred to hospice will be censored at 28 days—effectively, their TTR is infinity. A Cox proportional hazards regression model will be fit to estimate the rate ratio for recovery and its 95% confidence interval and to examine and adjust for the effects of covariates (remdesivir use, age, co-morbidities, and ordinal category status at the time of randomization).[62] The Cox procedure will also be used to model the dose-response relationship between TTR and tocilizumab dose. If the proportional hazards assumption

is violated,[63] as an alternative summary metric we will compare restricted mean survival times.[64,65]

Secondary time-to-event endpoints (overall survival and 28-day survival, 7-day TTR, length of hospital stay, TNEIMV, and TVIU) will calculated by the Kaplan-Meier method and compared between groups using a log-rank test.[60] In the analysis of hospital length of stay (LOS), patients who die or are discharged to hospice will be analyzed in two ways: (i) censored as of the date of death/discharge to hospice, and (ii) scored higher than the maximum LOS observed with the data analyzed using nonparametric, rank-based tests. Binary outcomes (Tmax response, RNEIMV, RVIU, CRP response, and secondary infection) will be compared between groups using chi-square and Fisher exact tests as well as logistic regression modeling to estimate odds ratios and to assess and adjust for the effects of covariates. DNEIMV and DVIU among those requiring ventilation and vasopressor/inotrope utilization, respectively, will be compared using two-sample t-tests. Since these comparisons condition on having had the event, nonparametric tests will also be performed in which patients without an event are assigned a score of 0. The duration of increased supplemental O_2 requirement from baseline will be treated as an ordinal variable and compared between groups by fitting proportional odds models.[66] Finally, adverse event rates will summarized by type, grade, and attribution to tocilizumab treatment and compared between groups using chi-square and Fisher exact tests.

10.4 **Interim Analyses**

An interim analysis will be performed after one-half of the targeted number of patients have been enrolled and followed for 28 days in the near-equivalence study to confirm that 400mg is not clearly better than the lower doses. The rate ratios for recovery will be compared between the 400mg and 120mg groups and between the 400mg and 40mg groups and a conservative O'Brien-Fleming boundary applied ($p < 0.0054$). If the boundary is exceeded for the 400mg vs. 120mg comparison, the trial will be terminated. If the boundary is exceeded for the 400mg vs. 40mg comparison, the 40mg dose will be dropped and 1:1 randomization performed between the 400mg and 120mg arms for the remainder of the study. Use of the O'Brien-Fleming boundary will lead to minimal power loss and allow the final analyses to be performed at the conventional 0.05 [0.025] level with negligible inflation of the type I error.

In the the superiority study, an interim analysis will likewise be performed after one-half of the patients have been randomized and followed for 28 days to compare TTR between the pooled tocilizumab dose arms and the 0mg control group using the O'Brien-Fleming boundary.

Finally, in both sub-studies we will assess wither the higher dosage(s) are associated with significant excess toxicity relative to the lower dose level(s). Specific toxicities to be monitored are grade 3 or 4 higher gastrointestinal perforation, liver injury, culture-proven bacterial infection (pneumonia or bacteremia), hepatotoxicity, neutropenia, or thrombocytopenia. Comparsions will be made using chi-square and Fisher exact tests

with the p-value for significance set at $p < 0.01$ to control for multiplicity. An independent Data and Safety Monitoring Board (DSMB) will be assembled to review the interim analyses.

11 STUDY MANAGEMENT AND REGULATORY AFFAIRS

11.1 Institutional Review Board (IRB) approval

The investigator will obtain, from the University of Chicago Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Chicago IRB of the deviation.

The University of Chicago IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).[67]

11.2 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on GCP; and relevant policies, requirements, and regulations of the University of Chicago IRB, University of Chicago and UCMC, State of Illinois, and applicable federal agencies.

11.3 Informed Consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor-investigator, will obtain the signed informed consent of each subject, prior to performing any study-specific procedures on the subject. The date and time that the subject signs the informed consent form will be recorded. The -investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial

changes to the clinical study or the risk-to-benefit ratio of study participation, the sponsor-investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

11.4 Data Safety Monitoring

11.4.1 Data Safety Monitoring by Study Investigators

The study investigators will meet at regular intervals throughout the trial as deemed necessary to review on-protocol and enrolled subjects of the clinical trial. Items that will be discussed will include (but not be limited to) the following:

- Enrollment rate relative to expectations, characteristics of participants
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants
- Adverse events

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

11.4.2 Independent Data Safety Monitoring Board

Unless otherwise specified, this protocol will undergo additional review by an independent DSMB composed of about 3-4 multi-disciplinary faculty from different institutions outside of University of Chicago Medical Center. This independent DSMB will likely include a pulmonologist/intensivist, rheumatologist, infectious disease specialist and a statistician well-versed in clinical trial methodology and protocols, COVID-19 and updated literature in addition to their subspecialty of expertise.

This Indepdent DSMB will convene via teleconference after the first 10 subjects are 3 days after drug dose and then at 10% enrollment, 25% enrollment, 50% enrollment and 75% enrollment, unless extenuating circumstances require meeting(s) otherwise.

As delineated by Clinial Trials Transformation Inititaive Recommendations, "DMC members will report any activities or connections with [trial investigators] that could be perceived as a conflict of interest. If any such activity or connection

is deemed to undermine the member's independence, that member may need to resign from the DMC." (www.ctti-clinicaltrials.org)

Recommendations and proposed modifications by the Indepdent DSMB will be relayed to this trial's predesignated leadership group which includes: Drs. Jennifer Pisano, Mary Strek, Mark Ratain, Theodore Karrison and Pankti Reid.

The DSMB will review in an unmasked fashion items related to (but not limited to) the following:

- Outcomes measures
- Recruitment progress
- Effectiveness of data collection
- Adherence to protocol
- Adverse events (serious, nonserious) and Mortality

11.5 **Amendments to the Protocol**

All modifications to the protocol or consent form will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. All participating sites will require approval of amendments made by Study Lead PI at University of Chicago.

11.6 **Annual IRB Renewals, Continuing Review and Final Reports**

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

11.7 **Record Retention**

Study documentation includes all case report forms (CRFs), data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

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