Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline			
Study Day	−2 to 0	1		2	
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (−4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)	36 hrs (±4 hrs)
Informed consent	x				
Inclusion/exclusion criteria	x	x			
Demographic data	x				
Randomization		x			
Medical history		x			
Complete physical examination [c]	x				
Weight		x			
COVID-19 diagnosis [d]	x				
Chest X-ray/CT scan [e]	x				
ECG	x				
Pregnancy test [f]	x				
PaO_2/FiO_2 [g]	x	← Optional →			
SpO_2 [h]	x	x	x	x	x
Vital signs [h]	x	x	x	x	x
Ordinal scoring [i]		x		x	
Adverse events [j]		x		x	
Concomitant medications [k]		x		x	

Appendix 1: Schedule of Activities: Days 1 and 2 (Cont.)

	Screening [a, b]	Baseline			
Study Day	−2 to 0	1		2	
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (−4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)	36 hrs (±4 hrs)
Hematology [l]	x	x		x	
Chemistry [m]	x	x		x	
Study drug administration [n]		x			
Central Labs					
Serum PD (CRP, IL-6, sIL-6R)		x [o]	x [o]	x	x
Serum PK [p]		x [q]	x [q]	x	x
Serum sample for exploratory biomarkers		x		x	
SARS-CoV-2 viral load [r]		x		x	
Serum SARS-CoV-2 antibody titer		x			
Cryopreserved PBMCs [s]		x		x	
Whole blood in PAXgene® tubes for RNA analyses [t]		x			

CRP = c-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; NEWS2 = National Early Warning Score; $PaO_2/FiO2$ = arterial oxygen partial pressure/fraction of inspired oxygen; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetic; PRO-CTCAE = NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; SpO_2 = peripheral capillary oxygen saturation.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within 48 hours before randomization may be used; such tests do not need to be repeated for screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified during the study should be reported as adverse events.

[d] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed within 7 days of randomization.

[e] Screening chest X-ray or CT scans should be performed within 48 hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

[f] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[g] If arterial blood gases are measured.

[h] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature), oxygen saturation and NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support) should be recorded together twice daily with approximately 12 hours in between while the patient remains hospitalized. If measured more than once during a 12-hour period, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[i] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1/Visit 1 then again daily every morning (between 8 am and 12 pm) for patients who remain hospitalized.

[j] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[k] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells; if the test is available at the site).

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

[n] Study drug should be administered after collection of all samples for pharmacodynamic and exploratory biomarker analyses. The initial study drug infusion should be given within 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

[o] On Day 1, CRP, IL-6, and sIL-6R samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion. Patents receiving a second infusion of study drug should provide extra samples for CRP, IL-6, and sIL-6R prior to and 15 minutes after the end of the infusion, on the opposite arm as the infusion.

[p] Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

[q] On Day 1, PK samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

[r] Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo bronchoalveolar lavage will have samples taken for virological assessment. It may only be possible to access one nostril if a patient has a nasogastric tube in place, in which case sites may collect a sample from one nostril only and where possible the same nostril should be used.

[s] For sites capable of sample collection for analysis of T cells by high-dimensional cytometry.

[t] The first draw of blood should not be for PAXgene® tubes to avoid contact with RNA preservation reagent inside the tube.