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BAT IT: Banked Anti-SARS Cov-2 T cell Infusions for Treatment of COVID 19

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CHECKLIST FOR PATIENT ELIGIBILITY AND NECESSARY INFORMATION:
PATIENT ID_____PATIENT NAME _____

YES	NO	VALUE/DATE	
Any "NO" answers will make a patient ineligible for study participation.			
			SARS-CoV-2 infection confirmed by PCR from a nasopharyngeal swab or other accepted specimen. (If testing was performed ≥ 5 days before enrollment, this must be repeated and accept only if positive again) Date of COVID test must be ≤ 5 days prior to infusion
			Currently hospitalized adult patient (≥18 years) requiring medical care for COVID19
			Peripheral oxygen saturation (SpO2) ≥ 92% on room air
			Hgb ≥ 7.0 gm/dl
			Negative pregnancy test (if applicable)
			Patient or parent/guardian capable of providing informed consent
			Evidence of pulmonary infiltrates on chest imaging
			High risk for requiring mechanical ventilation as defined by at least two of the following (circle all applicable): a. Age ≥ 60 years of age b. Age ≥ 75 years of age (counts as meeting **two** criteria) c. Hypertension d. Chronic cardiovascular disease other than HTN (eg: Coronary artery disease, congestive heart failure or cardiomyopathies). e. Diabetes Mellitus f. Obesity (BMI ≥30) g. Obesity (BMI ≥ 40, counts as meeting **two** criteria) h. Active cancer diagnosis or ongoing (within 3 months) of cytotoxic chemo/ radio-therapy for a cancer i. Post-hematopoeitic stem cell or solid organ transplantation status j. Immunodeficiency states as determined by the treating physician, including HIV infection on antiretroviral therapy (see protocol) k. Chronic obstructive pulmonary disease (COPD) l. Current everyday smoker m. Chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) n. Bronchial Asthma (on active treatment, eg: use of rescue inhalers etc.)
Any "YES" answers will make a patient ineligible for study participation.			
			Received ATG, Campath or other T cell immunosuppressive monoclonal antibodies in the 28 days prior to screening for enrollment
			Requiring mechanical ventilation at time of T cell infusion
			Alanine aminotransferase or aspartate aminotransferase > 5 x upper limit of normal
			If previous recipient of allogeneic hematopoietic stem cell transplant with evidence of active acute GVHD ≥ grade 2
			Uncontrolled relapse of malignancy
			Requiring vasopressors
			Known history of autoimmune disease except prior thyroiditis
			> grade 1 CRS, per ASTCT criteria

			Patients on > 6 mg/day of dexamethasone (IV) or equivalent
			Is not suitable at the discretion of the treating physician
			Patients should not be enrolled on any other interventional clinical trials for COVID19. Patients may receive routine care for COVID19 per institutional standards (including antivirals such as remdesivir or other FDA-EUA approved products and thromboprophylaxis).

Signature of MD _____ **Date** _____

1. BACKGROUND AND RATIONALE

1.1. COVID19.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and was first reported in Wuhan, China in December 2019. In January 2020, the World Health Organization (WHO) declared the outbreak a global emergency after rapid spread to multiple other countries including the United States, Italy, Japan, Iran and others. The number of cases continues to increase exponentially, surpassing 300,000 cases globally by March 23, 2020. SARS-CoV2 belongs to the Coronavirus (CoV) family, which also includes the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) that led to epidemics in 2003 and 2012, respectively. While COVID-19 shares a similar clinical presentation with SARS-CoV, it appears to have a different transmission rate (R0 2.2 in COVID-19 vs. around 3 with SARS-CoV) [1]. The most common clinical symptoms of COVID-19 at onset are fever, cough, dyspnea, myalgia, and/or fatigue. Less common symptoms included headache, diarrhea, nausea, and vomiting. However, the clinical spectrum ranges widely from asymptomatic or mild illness to critical illness in a subset of patients with progression to acute respiratory distress syndrome (ARDS), shock, and/or multi-organ failure leading to death [2]. As of late April 2020, there were over 2.5 million confirmed cases and over 150,000 deaths directly attributable to the disease worldwide, numbers that continue to rise [Worldmeter, Worldmeter-coronavirus].

1.2. Immune response to COVID19.

Death in many patients with COVID19 has been associated with a dysfunctional immune response wherein patients develop cytokine release syndrome (CRS) accompanied by severe ARDS leading to multiorgan failure and subsequent death [2]. In those who have died, persistence of virus in lung tissues coupled with ongoing widespread inflammation has been demonstrated [3]. Notably, in COVID patients requiring intensive care unit (ICU) support CD4+ and CD8+ T cell numbers have been found to be dramatically reduced (compared with milder disease cases) and the T cells that are present are terminally differentiated and exhausted (characterized by upregulation of markers such as PD-1 and Tim-3) [4-6]. This T cell deficiency may be due, at least in part, to the general immune dysfunction seen in severely ill patients, including elevated levels of suppressor cells (e.g. MDSCs) as well as increased levels of inhibitory cytokines including IL10 in serum [7]. We hypothesize that this T cell deficiency results in failure to clear the virus, and leads to an increased risk of patients requiring mechanical ventilation for ARDS and subsequent death.

1.3 Patients at risk of requiring mechanical ventilation from COVID19.

Based on a number of observational clinical studies of large cohorts (>1000 patients) the Centers for Disease Control (CDC) have compiled a list of risk factors, including concurrent chronic illnesses, older age, or immune dysregulation, which increase ones risk for complications from COVID19 including the need for mechanical ventilation or even death (**https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).**

Some of these factors such as older age, diabetes, heart disease, cancer, obesity, chronic renal insufficiency and COPD, etc often coexist in individuals. Not surprisingly, therefore, studies have shown that 2 or more coexisting illnesses greatly increases the risk for complications from COVID-19 compared with one illness alone [8]. Thus, we believe that those who have 2 coexisiting illness are at more likely to suffer COVID19 complications as compared with those who have one or none. Moreover, incremental advance in age can increase risk of death several fold starting at age 60 and up to 16-fold > 70 years of age;

furthermore, the risk related to body mass index (BMI) increases at a BMI of 30 (obese) to > 2.6 fold when BMI is > 40 (severely obese) [25].

The reason for this increased risk is unclear, though the elderly and those with suppressed or compromised immune systems exhibit weaker immune function than immunocompetent individuals, without overt immunodeficiency syndromes. For example, individuals >65 years of age mount sub-optimal immune responses to the annual influenza vaccine as well as to the virus itself, resulting in higher associated morbidity and mortality rates in this age group [9-12]. Thus, the CDC currently recommends use of a higher dose influenza vaccine in these individuals (https://www.cdc.gov/flu/highrisk/65over.htm).

As previously outlined (section 1.2) when patients get COVID-19, they demonstrate both numerical and functional T cell deficiencies that render them incapable of controlling and eradicating SARS-CoV-2-infected cells [4-8]. Thus, we believe that early intervention with the delivery of a potent, banked SARS-CoV-2-targeted virus-specific T cell (VST) product could improve outcomes for patients at risk of diease progression and death from COVID19.

1.4. Adoptive Immunotherapy with virus-specific T cells (VSTs)

Expansion of VSTs is clearly associated with eradication and protection from infection with viruses. Thus, adoptive immunotherapy to decrease the time to immune reconstitution is an attractive approach in patients at-risk for poor outcomes with COVID19. Virus-specific T cells generated by repeated stimulation with antigen presenting cells (APCs) expressing viral antigens have been evaluated in clinical trials to prevent and treat viral infections in immunocompromised hosts. This approach eliminates alloreactive T cells while expanding those that have specific activity toward the target viruses.

1.5. Banked SARS-COV2 allogeneic VSTs.

To generate SARS-CoV2 directed T cells for administration to patients at risk of developing COVID-19 we will prepare banks of allogeneic VSTs from individuals (healthy donors) that have been exposed to and cleared the virus. These banked VSTs will be available as an “off the shelf” product to those individuals that are partially HLA-matched with the donor and who are at risk of developing COVID. A concern with this approach is that in vivo persistence of a mismatched product may be suboptimal after administration, as the recipient may generate an immune response to the non-shared HLA antigens. However, a number of studies have demonstrated the feasibility of this approach and reported clinical responses in patients with EBV lymphoma arising after HSCT or solid organ transplant. In the first and largest multicenter study, Haque et al used banked polyclonal EBV-specific T-cell lines to treat EBV-PTLD after HSCT or solid organ transplantation and reported an overall response rate of 52% at 6 months [13]. Similar results have been reported from Memorial Sloan Kettering Cancer Center (MSKCC), with four of five PTLD patients achieving CR in response to third party EBV-specific T-cells [14]. Of note none of these studies reported an increased risk of GVHD.

Previously our group applied this approach to treat patients with refractory CMV, Adenovirus and EBV infections post allogeneic HSCT [15]. Lines were generated using adenovector-pp65 transduced monocytes and EBV-LCL and were either retained from our prior donor-specific clinical study or were newly generated from donors with known antiviral activity, including HLA homozygous donors identified by the National Marrow Donor Program. A total of 32 lines were produced and characterized, 18 of which were administered to the 50 study patients. The selection of lines for infusion was based on partial HLA match and the specificity of the line for the target virus.

This study was open to allogeneic HSCT recipients with CMV, AdV, or EBV infection that had persisted for at least 7 days despite standard therapy. Patients who had a suitable VST line received an intravenous infusion of up to 2×10^7 VSTs/m^2 and were eligible for additional infusions at intervals of at least 2 weeks, in the event of a partial response (PR). Of the 50 patients who received VST infusions 23 received VSTs for persistent CMV, 18 for persistent adenovirus, and 9 for refractory EBV-PTLD. Five of the 50 treated patients withdrew from the study or died of their underlying disease.

From the bank of 32 VST lines, a suitable line was identified for 90% of the screened patients within 24 hours. Of the 50 patients who were treated with these VSTs 74.0% had a CR or PR (73.9% for CMV, 77.8% for AdV, and 66.7% for EBV), including responses in 6 of 9 patients with refractory EBV-PTLD; most of these responses (89%) were durable. By contrast 8 patients in the study for whom a line was not available and who continued with "standard therapy" demonstrated a 13% response rate, and 6 (75%) died of viral disease.

More recently our group extended this "off the shelf" approach to five viruses using a T cell product manufactured in 10 days [16]. The VSTs were administered to 38 patients with 45 infections in a phase II clinical trial (CHARMS Clinical trial). A single infusion produced a cumulative complete or partial response rate of 92% (95% CI, 78.1% to 98.3%) overall and the following rates by virus type: 100% for BKV (n = 16), 94% for CMV (n = 17), 71% for AdV (n = 7), 100% for EBV (n = 2), and 67% for HHV-6 (n = 3). Clinical benefit was achieved in 31 patients treated for one infection and in seven patients treated for multiple coincident infections. Thirteen of 14 patients treated for BKV-associated hemorrhagic cystitis experienced complete resolution of gross hematuria by week 6. Infusions were safe, and only two occurrences of de novo GVHD (grade 1) were observed. VST tracking by epitope profiling revealed persistence of functional VSTs of third-party origin for up to 12 weeks.

Finally, in an industry supported single institution Phase I trial (VIRALYM-C) conducted at our institution, a minibank of normal donor VSTs directed against CMV was generated from only 8 donors and VSTs subsequently infused into 10 patients with mostly refractory CMV infections [17]. All infusions were well tolerated. Except for one patient who developed a transient isolated fever 8 hours after infusion, no cases of cytokine release syndrome (CRS) or other toxicities related to the infused CMVSTs were observed, and none of the patients developed graft failure, autoimmune hemolytic anemia or transplant associated microangiopathy. None of the patients developed recurrent or *de novo* acute or chronic GvHD post treatment.

All 10 infused patients responded to CMVSTs with 7 CRs and 3 PRs, for a cumulative response rate of 100% (95% CI: 69.2-100.0%) by week 6. The average plasma viral load reduction at week 6 was 89.8% (+/- 21.4%). The clinical and virological responses achieved in these patients were associated with an increase in virus-reactive CMVSTs in 8 of the 10 treated patients.

In conclusion, we believe administration of partially HLA-matched banked VSTs is safe and induces high response rates in patients with progressive viral illnesses. Therefore we hypothesize that a similar approach for COVID19 will reduce the overall morbidity and mortality of the patients. We propose to now generate a bank of SARS-CoV2-specific VSTs from healthy donors who have made a full recovery from COVID19. The resulting T cell lines would then be administered to patients that meet inclusion/exclusion criteria for this study.

1.6. Prior clinical evidence of risks associated with allogeneic VSTs.

In a study at MSKCC, 5 stem cell transplant (HSCT) patients received a median of 5 doses of third party EB-virus specific T cells (EB-VST) to treat EBV associated lymphoproliferative disease (EBV-LPD), most at $1x10^6$ EB-VST/kg/infusion, and all infusions were well tolerated [14]. Recently this group has published a larger experience reporting 46 recipients of HSCT (n=33) or solid organ transplants (SOT) (n=13) with established EBV associated lymphomas, who failed rituximab therapy and were treated with 3rd-party EBV-specific T cells. The cells were safe with only one patient developing grade I skin GVHD requiring topical therapy. Complete and sustained partial remissions were achieved in 68% of HSCT recipients and 54% of SOT recipients [18].

In our study of third party VSTs specific for three viruses (AdV, CMV and EBV) a total of 50 patients were infused with third party banked VSTs. All of the infusions were well tolerated [15]. There were no immediate adverse effects, and despite the HLA disparity between the VSTs and recipients, de novo GVHD occurred in only 2 patients (grade I in each case). In the 8 patients in whom acute GVHD developed within 45 days of the first infusion (grade I in 6 patients, grade II in 1 patient, and grade III in 1 patient), 6 had a history of GVHD prior to receiving the VSTs. An additional patient had a flare of chronic skin GVHD. Two patients experienced transplant-associated microangiopathy, a complication that occurs in up to 10% of HSCT recipients, particularly in those receiving sirolimus, as were both of our patients. Only 1 patient had secondary graft failure, concomitant with leukemic relapse.

In our subsequent Phase II CHARMS clinical trial [16], all infusions were well tolerated with no CRS. Nineteen patients (50%) had prior grade 2 to 4 GVHD (grade 2, n = 15; grade 3, n = 4), which was quiescent at the time of VST infusion. After infusion, one patient developed recurrent grade 3 GI GVHD after rapid corticosteroid taper, and five patients developed recurrent (n = 3) or de novo (n = 2) grade 1 to 2 skin GVHD, which resolved with the administration of topical treatments (n = 4) and reinitiation of corticosteroid treatment after a taper (n = 1). In long-term follow-up, two patients had a flare of upper-GI GVHD, which resolved after a brief corticosteroid course. Finally, one patient who received VSTs as treatment of BKV HC experienced transient hydronephrosis and a decrease in renal function associated with a concomitant bacterial urinary tract infection that resolved within 2 weeks.

In summary GVHD may occur after administration of allogeneic products, but in all cases (including in patients with compromised immune systems who are less able to reject allogeneic T cells), GVHD was of low grade and manageable. So we believe the risk for inducing GVHD in patients who have not undergone an allogeneic HSCT would be even lower than those reported above.

Another risk associated with administration of allogeneic products, not seen in clinical trials to date is the risk of myeloid aplasia induced by GVH reaction to the hematopoietic system. Our prior clinical experience indicates that this risk is minimal especially when the banked VSTs are administered to individuals with adaptive immune systems undamaged by prior chemotherapy or allogeneic HSCT.

Additionally, in our previous clinical trials utilizing allogeneic VSTs, outside of a near complete HLA-match (A-, B-, C-, DR- and DQ-), the persistence of partially HLA matched (minimum 2 allele match) in patients post-infusion is ~ 2 weeks. Even though post-transplant and cancer patients are relatively immunodeficient, there has been limited engraftment of

these types of cells for longer than 2 weeks and thus limited risks for developing prolonged GVHD or myeloid damage. The reason for this is allorejection of the infused VSTs.

1.7. Cytokine Release Syndrome.

There have been several reported SAEs associated with cytokine release syndrome (CRS) in patients who received T cells or bispecific T-cell engager therapies [19]. The majority of CRS have been reported after the infusion of CAR T cells [20], but CRS can also occur after the infusion of conventional antigen-specific T cells [21] or tumor infiltrating lymphocytes. Cytokine release syndrome is most likely in patients with very high viral burden [22]. Patients on the proposed study will be monitored closely as per study calendar and assessed for evidence of incipient CRS (onset of fever, malaise and dyspnea) and treated promptly. Management of CRS will follow published guidelines [23], and is described in more detail in SOP F 05.11.XX and includes treatment options based on the clinical severity of the symptoms, such as oxygen, inotropic agents, IL-6 receptor antibody (4-8 mg/kg), IL-1 receptor antibody and/or TNF-α antibody (5-10 mg/kg), and/or steroids (1-2 mg/kg/day of methylprednisolone or equivalent).

2. STUDY DESIGN.

This is a dose-finding safety followed by a randomized pilot trial comparing administration of SARS-CoVSTs vs standard of care to hospitalized patients with COVID19.

2.1. Primary Objective for dose finding phase.

This phase is designed to evaluate the maximum tolerated dose of partially HLA-matched SARS-CoVSTs administered to hospitalized COVID19 patients with high risk of progression to mechanical ventilation.

2.1.1 Primary end point: Dose-limiting toxicity (DLT) including GVHD, worsening CRS or ICANS and any other treatment-related toxicities as defined in Section 3.1 by day 14 post-infusion.

2.2. Primary Objective for randomized pilot trial phase.

To study the anti-COVID19 efficacy of administering banked partially HLA-matched SARS-CoVSTs to hospitalized COVID19 patients.

2.2.1 Primary end point: Response, defined as a ≥ 2 improvement in the WHO Ordinal Scale or discharge from hospital, by day 7 post-randomization. The scale is shown in Appendix III. Response data will be summarized by the proportion of patients in the treatment arm vs the control arm who have a response.

2.3. Secondary Objective for randomized pilot trial phase.

To confirm the safety of administering partially HLA-matched SARS-CoVSTs to hospitalized COVID19 patients with high risk of progression to mechanical ventilation.

2.3.1 Secondary end point: Treatment-related adverse events (tAE), including GVHD, worsening CRS or ICANS and any other treatment-related toxicities as defined in Section 3.1 by day 14 post-infusion in the treatment group.

2.4. Exploratory Objectives.

To study the clinical, immunological and biological effects of partially HLA-matched SARS-CoVSTs to hospitalized COVID19 patients. Outcomes will be compared and described for cancer and non-cancer patients.

2.4.1 Exploratory end points:

a. Expansion/persistence and in vivo effects of infused T cells assessed by a range of T cell measures
b. Endogenous immune reconstitution/antibody induction
c. Extended safety of T cell infusion to day 28 and 42 post-infusion
d. Incidence of Mechanical Ventilation [Time Frame: Up to 60 days]
e. Incidence of advanced ventilation (proning, oscillator or extracorporeal membrane oxygenation or use of inhaled pulmonary vasodilators) [Time Frame: Up to 60 days]
f. Ventilator-Free Days to Day 28 [Time Frame: Up to Day 28]
g. Organ Failure-Free Days to Day 28 [Time Frame: Up to Day 28]
h. Incidence of Intensive Care Unit (ICU) Stay [Time Frame: Up to 60 days]
i. Duration of ICU Stay [Time Frame: Up to 60 days]
j. Time to Clinical Failure [Time Frame: From time of infusion to time of death, mechanical ventilation, ICU admission, or study withdrawal (whichever occurs first, for up to 60 days)]
k. Overall Mortality [Time Frame: Up to 60 days]
l. Time to COVID-related Mortality [Time Frame: Up to 60 days]
m. Time to Hospital Discharge [Time Frame: Up to 60 days]
n. Incidence and duration of Supplemental Oxygen [Time Frame: Up to 60 days]
o. Time to Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) Virus Negativity [Time Frame: Up to 60 days]
p. Serum Concentration of biomarkers of T cell activation

2.4.2 Cancer Exploratory end points:

a) Incidence of Mechanical Ventilation [Time Frame: Up to 60 days]
b) Incidence of advanced ventilation (proning, oscillator or extracorporeal membrane oxygenation or use of inhaled pulmonary vasodilators) [Time Frame: Up to 60 days]
c) Ventilator-Free Days to Day 28 [Time Frame: Up to Day 28]
d) Organ Failure-Free Days to Day 28 [Time Frame: Up to Day 28]
e) Incidence of Intensive Care Unit (ICU) Stay [Time Frame: Up to 60 days]
f) Duration of ICU Stay [Time Frame: Up to 60 days]
g) Time to Clinical Failure [Time Frame: From time of infusion to time of death, mechanical ventilation, ICU admission, or study withdrawal (whichever occurs first, for up to 60 days)]
h) Overall Mortality [Time Frame: Up to 60 days]
i) Time to COVID-related Mortality [Time Frame: Up to 60 days]
j) Time to Hospital Discharge [Time Frame: Up to 60 days]
k) Incidence and duration of Supplemental Oxygen [Time Frame: Up to 60 days]

2.5. Rationale for Study Design and Dose Levels.

The primary purpose of the first phase of this study is to identify the maximum tolerated dose (MTD) of allogeneic SARS-CoVSTs for patients with COVID19. The study is a standard 3+3 safety study design. See Section 4 for details. Once the MTD is determined, the next phase of the study will commence. We plan to test 3 dose levels:

DL1: $1x10^7$ cells (flat dose)
DL2: $2x10^7$ cells (flat dose)
DL3: $4x10^7$ cells (flat dose)

These dose levels were selected because our prior clinical experience with allogeneic partially HLA-matched VSTs has demonstrated that a total dose of $4x10^7$ cells is safe. Since this will be first time patients with COVID19 who may have underlying immune dysregulation (lymphopenia etc), will be infused with banked VSTs we have taken the safety step of starting with 25% of the dose that has been shown to be safe in humans previously and escalate to $4x10^7$ in a 3+3 design.

Selected lines have to match at least two HLA alleles, although preference will be given to lines matching at the most loci.

The primary purpose of the randomized pilot study is to assess the efficacy of allogeneic SARS-CoV2-specific T cells in patients at risk of developing severe COVID-19. We will use the MTD as determined in the earlier phase for patients enrolled to this portion of the study. We plan to randomize enrolled patients to receive SARS-CoVSTs vs standard of care (SOC) treatments. The proportion of patients treated with VSTs vs SOC who have a clinical response (improvement) as defined in the protocol will be analyzed.

There are no FDA-approved treatments for COVID19 and establishing safety and simultaneously preliminary efficacy of this product for the treatment of COVID19 would be the first step toward examining the therapeutic potential of VSTs, which have proven to be effective in controlling a wide range of viral infections for which other treatments are unavailable.

2.6. Inclusion and Exclusion Criteria.

The same inclusion/exclusion criteria will apply to both phases of the study.

2.6.1. Inclusion Criteria.

1. SARS-CoV-2 infection confirmed by PCR from a nasopharyngeal swab or other accepted specimen type. (If testing was performed ≥ 5 days before enrollment, this must be repeated and accept only if positive again). Date of COVID test must be $\leq$ 5 days prior to infusion
2. Currently hospitalized adult patient (≥ 18 years of age) requiring medical care for COVID19
3. Peripheral oxygen saturation (SpO2) ≥ 92% on room air
4. Hgb ≥ 7.0 gm/dl
5. Negative pregnancy test (if applicable)
6. Patient or parent/guardian capable of providing informed consent (may be obtained electronically)
7. Evidence of pulmonary infiltrates on chest imaging. Any chest imaging findings which would be consistent with COVID19 would qualify (Eg: ground glass opacities, multifocal infiltrates etc.)

8. High risk of requiring mechanical ventilation as defined by at least *two of the following*:
   a. Age ≥ 60 years of age
   b. Age ≥ 75 years of age (counts as meeting **two** criteria)
   c. Hypertension
   d. Chronic cardiovascular disease other than HTN (eg: Coronary artery disease, congestive heart failure or cardiomyopathies).
   e. Diabetes Mellitus
   f. Obesity (BMI ≥ 30)
   g. Obesity (BMI ≥ 40, counts as meeting **two** criteria)
   h. Active cancer diagnosis or ongoing (within 3 months) cytotoxic chemo/ radio-therapy for a cancer
   i. Post-hematopoeitic stem cell or solid organ transplantation status
   j. Immunodeficiency states including HIV infection on antiretroviral therapy (except those listed as exclusion criteria #1, #7 and #10) as determined by the treating physician (eg: receiving immunosuppressive therapy like rituximab or congenital immunodeficiency syndromes, prior treatment with chemotherapy > 3 months ago but per investigators discretion could have lingering effects on the immune system, eg: chemotherapy regimens for lymphomas, ALL or AML etc.)
   k. Chronic obstructive pulmonary disease (COPD)
   l. Current everyday smoker
   m. Chronic kidney disease (eGFR < 30 mL/min/1.73 m^2)
   n. Bronchial asthma (on active treatment prior to admission, eg. Use of rescue inhalers or inhaled corticosteroids or other treatments to prevent/treat attacks).

2.6.2. Exclusion Criteria.

1. Received ATG, Campath or other T cell immunosuppressive monoclonal antibodies in the 28 days prior to screening for enrollment
2. Requiring mechanical ventilation at time of T cell infusion
3. Alanine aminotransferase or aspartate aminotransferase > 5 x upper limit of normal
4. If previously undergone an allogeneic HSCT and have evidence of active acute GVHD ≥ grade 2
5. Uncontrolled relapse of malignancy
6. Requiring vasopressors
7. Known history of autoimmune disease except prior thyroiditis
8. Is not suitable at the discretion of the treating physician
9. Patients on > 6 mg/day of dexamethasone (IV) per day or equivalent
10. > grade 1 CRS per ASTCT criteria
11. Patients should not be enrolled on any other interventional clinical trials for COVID19. Patients may receive routine care for COVID19 per institutional standards (including antivirals such as remdesivir or other FDA-EUA approved products and thromboprophylaxis).

2.6.3. Informed Consent and Randomization.

The informed consent process will begin at recognition of a subject who meets all eligibility criteria and consents to participation after a discussion with the study team (informed consent process). Consent may be obtained by teleconference. Once enrolled, blood will be taken from the subject for baseline immune response assessment and HLA-typing and if a partially HLA-matched VST line is available the subject will either receive treatment (dose escalation phase) or will be randomized (Randomized trial phase) to receive the partially matched VST line (in the treatment arm) or standard of care (in the control arm). If no VST line is identified, the patient will not proceed to treatment or randomization and will be removed from the study, but statistics on the proportion of patients who sign consent but are not treated or randomized will be reported.

Applicable only to the randomized phase, once randomized to the treatment arm, the patient must be infused with VSTs within 48 hours of randomization.

All consented patients will be registered in the online collaborative research environment (Forte's OnCore® eResearch CTMS), a Clinical Research Management System available at BCM Dan L. Duncan Comprehensive Cancer Center.

Enrollment to the dose escalation phase will be staggered. The first patient enrolled on each of the 3 dose levels (DL1, DL2 and DL3) will have to complete the 14-day toxicity monitoring window prior to enrollment of the next patients. Prior to dose escalation, all patients at a particular dose level should have completed the minimum 14-day toxicity monitoring window before enrolling to a higher dose level.

After the dose finding phase, patients will be randomized in a 1:1 ratio to receive SARS-CoVSTs at the MTD level or standard of care. Randomization will be performed in OnCore and use the permuted block method with a block size of 4 (2 in the treatment arm and 2 in the control arm). The purpose for a permuted block method is to ensure fairly random assignment during specific periods of surge with COVID19.

2.6.4. VST line manufacture and selection process.

Lines will be manufactured from individuals with common HLA types on an IRB approved protocol. We will approach donors that have previously had and recovered from a SARS-CoV2 infection.

For all banked lines, donors will be evaluated by one of the adult BMT physicians in the donor center at BCM who routinely evaluate donors for eligibility. Donors must meet standard eligibility criteria for donation of blood or marrow. They have been screened with the standard blood bank donor questionnaire, medical history and testing for infectious disease markers by a physician who is experienced in screening transplant/blood donors. The results of the physician assessment and ID testing are reviewed by a CAGT laboratory director who will give the final eligibility determination according to the SOP for Donor Evaluation. Only donors who have cleared this process and are deemed to be eligible will provide blood for VST generation.

We will generate T cell lines reactive against SARS-CoV2 using a modification of our published protocol [16]. Briefly, for the initial activation, research grade pepmixes spanning immunogenic structural and non-structural antigens will be used to directly stimulate PBMCs, followed by expansion in the presence of growth promoting cytokines and the G-Rex culture device, which supports in vitro T cell expansion. For the second stimulation autologous PBMCs are pulsed for 30 minutes with the same pepmixes, irradiated, and used to stimulate VSTs in the G-Rex device in medium supplemented with IL-2 (100 U/ml).

The VST lines will be checked for identity, phenotype and sterility, and cryopreserved prior to administration according to our SOP. To test the functional antigen specificity of the VST we will use individual pepmixes spanning each of the viral antigens used in the initial stimulation as a stimulus in IFNγ ELIspot/ELISA.

All cell culture manipulations will be carried out in the Center for Cell and Gene Therapy GMP facility using current standard operating procedures (SOPs). After Quality Assurance testing is complete a Certificate of Analysis will be issued.

Products that meet study specific release criteria, as detailed on the Certificate of Analysis, will be infused as per Section 2.6.2. Lines that match a minimum of 2 recipient HLA alleles will be used for infusion.

If a positive sterility testing result is reported after the product is infused, the FDA and other relevant parties will be notified as per our manufacturing SOP B01.03.XX (Product Quality Assurance Program and Release and Return of Clinical GMP/GTP Products) and clinical research SOP J02.06.XX (Serious Adverse Experience and Unanticipated Problem Reporting). Management of such a situation is further described in our SOP F05.09.XX (Management of Culture Positive Cell Therapy Products).

2.6.5. Administration and Monitoring.
Partially HLA-matched VSTs will be thawed and given by intravenous injection (in a syringe or a bag). Patients will receive partially HLA-matched VSTs as a single infusion. In the rare case where insufficient banked cell product is available, a lower number of cells may be infused with agreement of the principal investigator, patient and/or guardian and the treatment team.

2.6.5.1. Premedications. Patients without prior history of reaction to blood products generally do not require premedication. If patients receive premedication, Benadryl iv/po and/or Tylenol po/iv may be given at doses appropriate for recipient size.

2.6.5.2. Monitoring immediately post-infusion. Patients will be monitored according to institutional standards for administration of blood products and at a minimum will be monitored according to below:

- Patients should remain on continuous pulse oximetry for at least 30 minutes
- Vital signs should be monitored at the end of infusion then at 30 and 60 minutes

2.6.5.3. Supportive Care. Patients will receive supportive care for acute or chronic toxicity, including infusion reaction, antibiotics and as indicated antipyretics for fevers, and other interventions as appropriate.

2.7. Standard of care arm (only for the randomized phase of this study).
Patients randomized to the standard of care arm will continue to receive treatments for COVID19 as determined by institutional protocols. They will not receive a placebo.

2.8. Risks and Mitigation strategies for Toxicities in the Treatment Arm.

2.8.1. Graft Versus Host Disease (GVHD).

The risk that adoptively transferred partially HLA-matched VSTs will cause Grade II or higher GVHD is low in these patients, the majority of whom will be partially or fully immunocompetent. According to data from previous studies [15, 16] even allogeneic transplant recipients whose immune function is substantially impaired had a low frequency of significant GVHD after treatment with 3rd party VSTs specific for adenovirus, EBV, CMV, BK and HHV6 (Section 1.6). If any subject develops GVHD they will receive our standard GVHD treatment as per SOP F08.03. GVHD will be monitored for 2 weeks following infusion. Weekly GVHD organ stage scores (up to 2 weeks post infusion), overall clinical grade, biopsy information for GVHD and relevant differential diagnosis will be recorded. The weekly score will encompass all information since the last assessment. Organ involvement, biopsy information, staging, differential diagnosis, and GVHD therapy will be documented in the medical record using the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) GVHD scoring stamp or equivalent.

2.8.2. Cytokine Release Syndrome (CRS).

Patients with COVID19 have developed cytokine release syndrome secondary to a dysfunctional immune response in individual patients [2]. Genetically modified T cell immunotherapies have also been associated with CRS and so it is possible that patients who receive infusions of SARS-CoV2 specific T cells could develop or worsen CRS. Therefore we anticipate this toxicity in COVID19 treated patients and intend to grade the CRS according to ASTCT criteria (Appendix 1) [23]. Similarly, genetically modified T cell infusions in cancer patients have been associated with neurological toxicities (known as ICANS: immune effector cell associated neurological toxicity) and it is possible that patients treated on this study could develop ICANS and thus we plan to grade this using ASTCT criteria [23]. Certificate of Analysis rules for CRS/ICANS as graded by ASTCT and any other toxicity that should arise (e.g. severe local reactions or hepatorenal damage) as graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5 are described in the section below.

2.8.3. Additional considerations.

(i) All female patients who are not exempt (older than 55 or have had a prior sterilization treatment) will undergo a pregnancy test (paid by research) prior to study enrollment. *(ii)* We do not expect that this therapy would complicate future blood product transfusions or need for extracorporeal membrane oxygenations. There have been no reported special complications with subsequent blood product transfusions or use of extracorporeal membrane oxygenation in patients receiving allogeneic T cell (administered to >500 recipients worldwide) or stem cell products (>10000 recipients worldwide).

2.8.4. Management of any untoward toxicities.

VSTs are susceptible to killing by steroids given at a dose of 1-2mg/kg. This is standard therapy for GVHD and could also be given if a recipient develops other complications considered possibly related to VST administration. Anti IL-1R and anti IL-6R infusion may also be used for ICANS or CRS respectively and will be considered in patients with grade II or higher CRS (ASTCT criteria) (see SOP: F05.11.4 MANAGEMENT OF ADVERSE REACTIONS TO CTL INFUSIONS for dosage details). Other supportive care would be per standard medical practice.

3. PATIENT EVALUATION

3.1. Safety

Patients will be closely monitored for a minimum of 14 days for toxicities or until all treatment related toxicities have resolved. Except as noted below (in section 3.4.1), the safety endpoint [dose limiting toxicities (DLT) for the dose escalation phase or treatment-related adverse event (tAE) for the randomized phase] will be defined as any acute GvHD (grade ≥ 3), grade ≥3 CRS or ICANS, grade ≥3 hematologic toxicity or grade ≥3 non-hematologic adverse events related to the T cell product within 14 days of the VST infusion and that are not due to pre-existing conditions as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

3.2. Antiviral Activity.

We will assess the efficacy of SARS-CoV2 specific T cells by comparing the proportion of patients in the treatment arm with those in the control arm (only during the randomized phase of the study) who have a clinical response by day 7 post-randomization (measured as an improvement in their WHO ordinal scale score by 2 or more points or if the patients gets discharged from hospital). When available radiographic response information will also be compared between both groups as well as several other exploratory end-points as listed in section 2.3.

The schedule of monitoring for safety and antiviral activity is demonstrated below.

Table 1. REQUIRED ASSESSMENTS					
	Day-5 to Day -1 (pre-infusion)	Day 0	Days 1-14 (daily)	Days 15 to resolution of treatment-related toxicity (if applicable)	Month 2, 3 and 6
Consent, COVID testing and HLA-typing (research test)	X				
T cell infusion (dose escalation phase) or Randomization[3] (randomized phase) (research)		X			
History		X	X**	X	X
Acute GVHD and CRS/ICANS evaluation (research)[$]		X[$]	X*	X*	
Chemistries: Liver function tests (alkaline phosphatase, bilirubin, AST, ALT), ferritin, DDimer, LDH and CRP[$]		X	X*/**	X*	
Pregnancy test (research)[1]	X				
Infusion related toxicity evaluation (research)[$]		X	X*/**	X*	
Clinical response assessment (WHO ordinal scale)		X	X**	X*	
Chest imaging	X (within 48 hrs of randomization)		X** (at least once post infusion)		
Blood and serum for ancillary laboratory studies (research)[2]		X	X*/**	X*	X***
CBC with Differential		X	X*/**	X*	X***
Basic Chemistry		X	X*/**	X*	X***

*At a minimum weekly assessments needed until resolution of all treatment-related toxicities

**Until discharge from hospital

***2, 3 and 6 month labs optional and billed to research if performed; history may be obtained via telephone if necessary, off study will be assessed per criteria in Section 4.3.2.

$: Not required for patients randomized to the standard of care arm (control arm)

1: Pregnancy test where applicable (research test)

2: Research procedures beyond that required for usual care - 30-40mls or 6-8 teaspoons may be collected at each time point. Depending on clinical and laboratory responses samples may be collected at additional time points

3: T cells must be infused within 48 hours of randomization.

Research laboratory studies may include:
Assessment of virus-specific immunity as measured by serum profiling, ELIspot/ELISA/cytokine profiling, intracellular cytokine staining, multimer assays, TCR deep sequencing and/or other assays as they become available

3.3. Assessments during the study.

The timing of events as per the schedule in Table 1 above is based on the date of receiving VST infusion (dose escalation phase) or from randomization (randomized phase). Additional follow up assessments may be done based on clinical and laboratory responses.

All assessments are considered standard-of-care unless identified.

Pre-treatment/Randomization.

1. Consenting
2. Patient HLA-typing to identify a suitably matched VST line
3. Confirmation of positive COVID test within 5 days of informed consenting
4. Pregnancy test* if female patient of childbearing potential and (if a transplant recipient) has received a reduced intensity transplant regimen
5. Chest radiograph if not already done in the past 48 hours.

Day of Treatment/Randomization.

1. History and physical exam including height and weight
2. CBC with differential
3. Basic chemistry
4. Chemistries: liver function tests (bilirubin, alkaline phosphatase, AST, ALT), ferritin, DDimer, LDH and CRP
5. Blood and serum for ancillary lab studies
6. T cell infusion in the treatment arm of the randomized phase of the study should occur within 48 hours of assignment to treatment arm.
7. Acute GVHD and CRS/ICANS evaluation (only for treatment arm)

Post-Treatment/Randomization.

1. Daily Clinical improvement as measured by the ordinal scale (until day 14)
2. Daily history, collect blood and serum for ancillary lab studies, and CBC with differential (until day 14 or until discharge from hospital whichever comes first, refer to Table 1 for more details)
3. Chest-imaging (at least once post infusion by day 14)
4. Case Report Form (CRF) to include:
   a. Complete acute GVHD staging and grading information (including skin, liver, upper and lower GI) assessed at a minimum weekly for the first 2 weeks and longer until resolution of GVHD if it develops (only for treatment arm).
   b. Chemistries: liver function tests (bilirubin, alkaline phosphatase, AST, ALT), ferritin, DDimer, LDH and CRP, done at least weekly while hospitalized. If discharged no further chemistry testing is necessary.
   c. Infusion-related toxicities assessed at a minimum weekly for the first 2 weeks and longer until resolution of any treatment related adverse events. (only treatment arm). This must include at least weekly assessment of immune effector related toxicities like CRS/ICANS per ASTCT grading.

Late follow-up visits (at months 2, 3 and 6), if outpatient:

1. History: in the BMT clinic on Walter Tower 15 (Houston Methodist Hospital). Can alternatively be done via teleconference
2. Laboratory studies: Optional for these visits. If collected then will be performed at the BMT clinc on Walter 15 (Houston Methodist Hospital).

3. Findings which are deemed to be treatment related at these late follow-up visits will be managed by infectious diseases and cell therapy trained attendings (Principal and co-investigators on study) at Houston Methodist Hospital.

There are no plans for compensation for injuries related to this study.

3.4. Modified Follow-Up, Off-study & Stopping rules.

3.4.1. Criteria for placing study on hold.

3.4.1.1. Any patient who develops Grade ≥3 acute GVHD or Grade ≥3 treatment-related (at least possibly related) adverse event, excluding CRS or ICANS, post VST infusion. In such patients, the toxicities will be followed until resolution or until their off study date but no new patients will be treated until reviewed by the data safety board and reported to the FDA. For the purposes of the dose escalation phase of this study this would qualify as a DLT.

3.4.1.2. Any patient who experiences grade ≥3 CRS or ICANS that persists beyond 72 hours and worsens despite 2 doses of tocilizumab/Anakinra treatment irrespective of attribution to VSTs. In such patients, the toxicity will be followed until resolution or until their off study date. For the purposes of the dose escalation phase of this study this would qualify as a DLT.

3.4.1.3. Any patient who experiences grade II acute GVHD that persists >14 days from onset or which is refractory to systemic steroid treatment (defined as no improvement in overall grade within 7 days of initiation of systemic steroids at 2 mg/kg/day). For the purposes of the dose escalation phase of this study this would qualify as a DLT.

3.4.1.4. If the first 2 patients treated at any DL or any 2 consecutively treated patients that receive VSTs during the randomized phase experience grade $\geq$ II CRS or ICANS that persists for 7 days or is non-responsive to 2 doses of tocilizumab/Anakinra irrespective of attribution. For the purposes of the dose escalation phase of this study this would exceed the DLT boundary and would then study 3 additional patients at a lower dose level or if this were to occur on DL1 would stop accrual until a review is conducted.

Patients who meet these criteria will remain on follow-up as per the required assessments Table 1.

3.4.2. Procedures after stopping study.

Once stopped, the study team will review the outcomes of the patients infused and report to regulatory authorities for review. The study will not resume until approvals to continue are granted by the study team and regulatory authorities including the IRB, DSMB and FDA.

3.4.3. Off Study Criteria

3.4.3.1. Completion of study specified procedures.
3.4.3.2. Refusal of further study follow-up by patient or legal guardian.
3.4.3.3. Lost to follow up.
3.4.3.4. Death

4. STATISTICAL CONSIDERATIONS

4.1. Study Design Synopsis

This study is a dose-finding safety study followed by a randomized, controlled pilot study to evaluate the safety and clinical effects of administering banked partially HLA matched SARS-CoVSTs to hospitalized COVID19 patients.

4.2 Dose Finding Phase

Three dose levels will be evaluated (Section 2.5). Dose escalation will be guided by the standard 3+3 design in order to determine the maximum tolerated dose (MTD) of SARS-CoVSTs. Detailed definitions of DLT are described in Section 3.1 and Section 3.4.1. The specific procedure is as follows: Starting from dose level 1 and escalating to the highest level sequentially, a cohort of three patients will be enrolled at each dose level, with a stagger to wait until the first patient on each dose level completes the 14-day toxicity monitoring window prior to enrollment of the other two patients. Dose level to the subsequent new cohort will not be assigned until the patients in the previous cohort have finished their 14-day period and their toxicity evaluations have become available. If no DLT is observed in any of the first 3 patients, the dose level will be escalated to the next dose level. If DLT is observed in 1 of the 3 patients, 3 more patients will be enrolled at the same dose level. If DLT is observed in no more than 1 out of 6 patients then we will advance to the next dose level. If DLT is observed in 2 or more patients at a same dose level then the MTD has been exceeded and the next lower dose level will be considered as the MTD level, if 6 patients have already been treated at that level. If only 3 patients have been studied at the MTD, 3 more patients will be enrolled at the MTD level to confirm that no more than 1 out of 6 patients have a DLT. Escalation will not proceed past dose level 3. If none of the dose levels has more than one patient who develops a DLT, then the highest dose level will be defined as the MTD. Patients who develop DLTs or complete 14-day monitoring periods after the VST infusion are considered DLT evaluable. Any patients who drops off the study early before day 14 due to a non-DLT-related reason will be replaced.

4.3 Randomized Pilot Trial Phase

After the MTD is determined, the study will continue to the randomized pilot trial phase. Consented and eligible patients in this phase will be randomized in a 1:1 ratio to receive either SARS-CoVSTs on the MTD level or standard of care. Randomization will employ the permuted blocks method with a block size of 4 (2 in the treatment arm and 2 in the control arm). No stratification will be used in randomization.

In the randomized pilot trial phase, we will continuously monitor the safety of SARS-CoVST infusions in the treatment arm so that the accual can be halted early if there is an unexpectedly high rate of treatment-related adverse events. Treatment-related adverse events (tAE) are defined in Section 3.1. Every patient who is randomized to the treatment arm and infused with SARS-CoVSTs will be evaluated for tAE and all patients who have tAEs will be followed until toxicities resolve. A tAE rate of greater than or equal to 25% is considered excessive. The occurrence of tAEs will be monitored using a stopping guideline based on a Pocock-type boundary method [24]. The following sequential stopping boundaries will be used:

Number of Patients	1-2	3	4-5	6-7	8-9	10-12	13-15	16-17	18-20
Number of tAEs <	-	3	4	5	6	7	8	9	10

The accrual will be halted if the number of tAEs is equal to or exceeds the boundary in the above table. Under this sequential stopping rule, the probability of early stopping is 5% if the true tAE rate is 25%, and the probability of early stopping will be high at 67.5% if the true tAE rate is 50%.

4.4 Stopping Rules

Per Section 3.4.1, halting rules for the study have been defined and these align with DLTs. The study will not resume until approval to continue are granted by the study team and regulatory authorities including the IRB, DSMB and FDA.

4.5. Sample Size Determination and Design Characteristics

A maximum of 18 DLT evaluable patients will be accrued to the dose finding phase of the study. Based on our previous studies and experiences, we do not anticipate seeing any VST-related AE at any dose level and we expect to enroll 12 for the phase.

In the randomizaed pilot trial phase, a total of 40 patients will be enrolled and randomized (20 in the treatment arm and 20 in the standard of care arm). The safety endpoint in this phase is tAE. The study is designed to monitor toxicity due to SARS-CoVSTs closely so the trial can halt accrual early if its toxicity rate is excessive. For this purpose, a tAE rate of 25% is considered excessive, while a rate below 25% is considered acceptable. Based our current experience with VST therapy, we anticipate the actual tAE rate to be much lower around 5%. With 20 patients in the treatment arm, if the observed tAE rate is 5%, the corresponding 95% confidence interval will be 0.1%-24.9% which excludes 25%, and the chance of observing more than 3 tAEs in the treatment arm is only about 1.6%. The efficacy endpoint in this phase is clinical response, defined as improvement in at least 2 points in the WHO Ordinal Scale or discharge from hospital by day 7 post randomization. Patients' outcome will be dichotomized as 'having a response' or 'not having a response'. Patients who died before day 7 will be deemed as 'not having a reponse". Based on current publications of novel COVID-19, we expect 90% patients in the treatment arm and 50% patients in the control arm will have a response by day 7. A sample size of 40 will provide 83% power to detect the 40% increase in response rate for the SARS-CoVSTs treatment compared to the standard of care treatment, with a Fisher's exact test at a 5% one-sided significance level.

We anticipate about one third subjects who are considered for study participation will not meet all inclusion criteria, thus we will consent 87 subjects to have 58 eligible patients (18 in dose finding phase and 40 in the randomized pilot trial phase).

4.6. Data Analysis

All patients who received VSTs infusions or standard of care will be included in the safety analyses. All patients infused with SARS-CoVSTs and finish their 14-day toxicity observation or develop a DLT/tAE before day 14 are considered DLT/tAE evaluable. All efficacy analysis will be based on the intent to treat (ITT) population, defined as eligible and randomized subjects.

Adverse events and corresponding toxicity grades after study treatment will be summarized descriptively by phases then arms. Toxicity information including the type, severity, time of onset, time of resolution, and the probable association with study treatments will be tabulated and summarized. Incidence of DLT/tAE in patients who receive VST infusionsdefined in Section 3.1 and 3.4.1, will be reported with rates and 95% binomial exact confidence intervals.

Clinical responses will be summarized using rates and 95% binomial exact confidence intervals for the randomized pilot trial phase by arms and compared using Fisher's exact test. Anti-COVID19 efficacy assessed by the WHO ordinal scale will be evaluated every day up to day 14 post-randomization. The assessments will be summarized using descriptive statistics such as medians and ranges. Plots of the assessments over time will be generated for each patient to graphically illustrate the pattern and trend of clinical staus. The changes in scales by day 14 post randomization will also be computed; percentages of patients with stable ordinal scale, with worse or improved scales will be summarized by arms.

Clinical exploratory end points (requirement of supplemental oxygen, progression to mechanical or advanced ventilation or ICU, mortality rate, duration on oxygen supplementation, duration of ventilation free, duration of organ failure-free, durations of ICU stay and hospital stay, time to RT-PCR virus negativity) will be summarized in a descriptive nature by arms. Categorical variables will be summarized by frequencies and percentages, and continuous variables will be summarized by means, standard deviations, medians, interquartile ranges. Clinical endpoints will be compared between arms using Fisher's exact tests or Wilcoxon rank sum tests, whichever is appropriate. All statistical tests for clinical exploratory endpoints will be considered exploratory

Time to clinical failure is defined as the days from VST infusion to date of death, mechanical ventilation, ICU admission, or study withdrawal, whichever occurs first. Patients without those clinical failure events up to 14 days will be considered censored. Time to clinical failure will be estimated in each arm by the Kaplan-Meier method and compared using log-rank tests.

Laboratory data, which include expansion and persistence of infused VSTs, inflammatory markers, biomarkers of T cell activation, will be summarized with appropriate summary statistics . Changes from pre- to post-infusion will be plotted for each patient who receives the VST infusionover time and assessed using paired comparisons when appropriate.

5. REPORTING REQUIREMENTS

5.1. Registration

Register all patients with Cell and Gene Therapy Research Coordinator.

The following data will be collected:

Eligibility
On study
Concomitant medication
Off study
Response
Adverse event
CRS/ICANS Adverse Events (as applicable)
Death

5.2. Drug Toxicity and/or Adverse Reactions.

5.2.1. Adverse events will be collected as per SOP J 02.05.XX and J02.75.XX. Data on adverse experiences/toxicities regardless of seriousness must be collected for documentation purposes only for 14 days after the last dosing of the study drug/biologic

with the exception of all toxicities which were deemed to be related to the infusion and will be followed until resolved.

5.2.2. Serious adverse events will be collected and reported as per SOP J 02.06.XX until 3 months after the last dosing of study drug/biologic.

5.3. Informed Consent.
All patents and/or their legal guardian must sign a document of informed consent consistent with local institutional and Federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed, and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by him or his legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines

5.4. Clinical Trial Oversight & Monitoring
This protocol will be conducted in accordance with the Cell and Gene Therapy Monitoring Plan on file with the FDA.

This protocol will be monitored in accordance with the current Data Safety Monitoring Plan of the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine.

The conduct of this clinical trial will be evaluated in accordance with the Texas Children's Cancer Center and Center for Cell and Gene Therapy Quality Assurance Policy and Procedure Plan.

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Appendix I

Appendix I CRS Grading Scale per ASTCT guidelines

Grade	Symptoms
1	• Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise)
2	• Symptoms require and respond to moderate intervention • Oxygen requirement <40% or hypotension responsive to fluids or • low dose of one vasopressor or Grade 2 organ toxicity
3	• Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% or hypotension requiring high dose or multiple vasopressors or • Grade 3 organ toxicity or Grade 4 transaminitis
4	• Life-threatening symptoms • Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	• Death

Appendix II

MAGIC Critera for Staging and Grading of Acute GVHD

Outside of the MAGIC criteria listed in the table below, marrow aplasia as part of GVHD can occur outside of the context of an allogeneic HSCT. So to monitor for marrow aplasia, we will follow CTCAE version 5 for grading of hematologic toxicitiy. Stopping rules for prolonged or serious marrow aplasia and/or GVHD or other toxicities are detailed above.

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

Appendix III

[https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.]

The ordinal scale is an assessment of the clinical status at a given day. Each day, the worst score from the previous day will be recorded.

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8