Official Title:	Pharmacokinetics of a SARS-CoV-2 Monoclonal Antibody in Hematopoietic Stem Cell Transplant Recipients
NCT Number:	NCT05135650
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	7/17/2023

FRED HUTCHINSON CANCER CENTER
UNIVERSITY OF WASHINGTON MEDICAL CENTER

Title of Protocol:
Pharmacokinetics of a SARS-CoV-2 Monoclonal Antibody in Hematopoietic Stem Cell Transplant Recipients (COVIDMAB)

Current date: 07/17/2023
Previous date: 06/30/2022

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PROTOCOL SYNOPSIS

Protocol Number: 10691	**Product Names:** VIR-7831 (Sotrovimab)
Title of Study: Pharmacokinetics of a SARS-CoV-2 Monoclonal Antibody in Hematopoietic Stem Cell Transplant Recipients **PI:** Alpana Waghmare, MD	
Sponsor-Investigator: Alpana Waghmare, MD	**Phase of Development:** Phase 1

Study Objectives: To assess the pharmacokinetics of the anti-SARS-CoV-2 monoclonal antibody (mAb) VIR-7831 up to six months post-transplant in hematopoietic stem cell transplant (HCT) recipients.

Primary: To determine the levels of VIR-7831 mAb post-transplant in serum over time.

Secondary:
1. To compare the half-life of VIR-7831 in autologous vs. allogeneic transplant, cord vs. non-cord allogeneic transplant, matched vs mis-matched donors, in patients with and without GVHD, and in patients with and without diarrhea
2. To monitor the frequency of breakthrough SARS-CoV-2 acquisition in HCT recipients who have received VIR-7831
3. To compare antibody levels from serum collected by venipuncture versus self-collected using a TASSO device.
4. To monitor the development of anti-drug antibodies
5. To monitor safety with routine labs as part of standard post-transplant care.
6. Exploratory: To measure VIR-7831 and SARS-CoV-2 neutralizing antibodies in nasal swabs and SARS-CoV-2 neutralizing antibodies in serum.

Study Purpose and Rationale:

Respiratory viral infections cause significant mortality, morbidity, and health care costs in the immunocompromised HCT population. The current pandemic caused by the novel coronavirus SARS-CoV-2 poses a threat to this vulnerable population. HCT recipients are most vulnerable to infection during the early post-transplant period; however, vaccination is also thought to be ineffective during this period because the immune system is not yet fully reconstituted. Current guidelines recommend considering vaccination at least three months after transplant even though efficacy may be sub-optimal. Monoclonal antibodies (mAbs) against SARS-CoV-2 administered pre-transplant represent a strategy to reduce the risk of COVID-19 among HCT recipients. Several mAb candidates against SARS-CoV-2 are advancing through clinical trials. VIR-7831 is an extended half-life mAb was granted Emergency Use Authorization by the Food and Drug Administration (FDA) in May 2021 for early treatment, based on the recently completed phase 3 COMET-ICE clinical trial (NCT04545060) demonstrating an 85% reduction in hospitalization or death when VIR-7831 was given early after infection as monotherapy.

This study seeks to define the pharmacokinetics of VIR-7831 against SARS-CoV-2 with regards to half-life in the serum and the impact of HLA-mismatch and GVHD on these kinetics in transplant recipients. Evidence exists in the literature suggesting that the half-life of CMV- and RSV-specific antibodies is significantly shortened in HCT recipients, and particularly in those who received an allogeneic transplant. One possible explanation for this phenomenon is accelerated antibody loss through GVHD-related gut leakage. A better understanding of the kinetics of antibody decay in the serum could help determine the utility of immunoprophylaxis in bridging this window of vulnerability.

Study Population:

This is a prospective, open-label, single arm study that will enroll a target of 50 subjects prior to HCT. We will enroll patients who are pre-transplant and have completed a transplant arrival visit and who meet other eligibility criteria (detailed below). Participants will receive one 2,000 mg dose intravenously of VIR-7831 within one week (seven days) prior to the start of conditioning, and the mAb will be infused at least 24 hours prior to the start of conditioning, i.e. mAb infusion will occur within 1-7 days prior to conditioning).

Patient Inclusion Criteria:

- Age at least 18 years of age
- Undergoing HCT (any donor or stem cell source, including autologous or cord blood transplant)

- History of prior transplants is permitted
- History of COVID-19, positive PCR of a respiratory specimen for SARS-CoV-2 as long as it is not within four weeks from conditioning, or seropositivity for SARS-CoV-2 is permitted
- History of SARS-CoV-2 infection or vaccination of the donor are permitted.
- Able to provide informed consent
- Post-enrollment vaccination is anticipated and permitted
- Administration of IVIG before or during the study is permitted

Patient Exclusion Criteria:

- Positive PCR result for SARS-CoV-2 within four weeks of scheduled conditioning
- Signs or symptoms of uncontrolled active infection
- Pregnant or breastfeeding
    - Pregnancy test is obtained as part of pre-transplant evaluation in women of child-bearing potential at arrival to transplant and again within 7 days of conditioning and will be confirmed as negative by review of the chart
- Previous known allergies to any component of VIR-7831
- Previous anaphylaxis or severe hypersensitivity reaction, including angioedema, to a mAb
- Participants of other clinical studies that preclude the use of other investigational compounds
- Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol or unlikely to survive to the end of study

Test Product, Dose, and Mode of Administration:

Product: VIR-7831

Dose: 2,000 mg mAb

Mode of Administration: Intravenous infusion over approximately 60 minutes.

Timing of Administration: Within one week prior to the start of conditioning.

VIR-7831 is a fully human immunoglobulin G1 kappa (IgG1κ) mAb derived from the parental mAb S309, a potent neutralizing mAb directed against the spike protein of SARS-CoV-2. S309 binds to a highly conserved epitope of the SARS-CoV and SARS-CoV-2 spike protein receptor binding domain (RBD) and inhibits SARS-CoV-2 infection in vitro. The Fc region of the molecule contains the 2 amino acid Fc-modification LS, designed to provide extended half-life and enhanced biodistribution to the lung. VIR-7831 is provided as a sterile liquid for intravenous infusion or intramuscular injection. All clinical study materials are manufactured in accordance with current Good Manufacturing Practice (cGMP) regulations. VIR-7831 has been tested in the phase 3 COMET-ICE clinical trial and reduced hospitalization and death when used as early treatment for COVID-19.

Clinical Observations and Safety Assessments. Clinical evaluation will occur immediately prior to mAb administration. Participants will complete a weekly symptom questionnaire prior to and weekly after mAb administration for a total 24 weeks. Safety assessments will be performed with routine labs as part of standard stem cell transplant care.

Biomarker Assessments: Immediately prior to mAb administration and at the end-of-infusion, weekly up to week 4, monthly up to week 12, and at week 24 after mAb administration, blood will be drawn by venipuncture (10-20 mL per blood draw) by nursing, a phlebotomist, or trained study staff. At week 12, and monthly thereafter to the end of primary end-point (week 24), blood is self-collected using a TASSO device and by venous blood draw. Nasal specimens will be collected by mid-nasal foam swab at the same time-points as blood draws. Nasal swabs and blood via TASSO (or venous blood draw) will also be collected off-schedule for SARS-CoV-2 PCR and antibody testing as needed based on respiratory symptoms (answering yes to one or more of the nose or chest symptoms) within 48 hours of symptom of symptom onset, up to week 36. If positive for SARS-CoV-2, weekly nasal swabs will be obtained longitudinally for SARS-CoV-2 PCR until negative or until week 36. Serum, plasma, or nasal swabs will be processed and stored at either 4°C, at -20°C, or at -70°C until use, as appropriate. Testing will include serum and nasal total IgG, VIR-7831, SARS-CoV-2-specific IgG, SARS-CoV-2 neutralization titers, and anti-drug antibodies. Testing will be performed at the Fred Hutch, UW, or by Vir Biotechnology.

Statistical Methods:

The target enrollment for this trial is 50 pre-hematopoietic stem cell transplant candidates. Twenty subjects have already been infused with a 500 mg dose. Thirty additional subjects will be infused with the 2,000 mg dose. Descriptive statistics will be used to analyze the data. An exponential decay model will be used to calculate half-life.
Sample size and estimated duration of the study: Based on the estimated number of treated patients meeting primary eligibility criteria per year and an estimated 35% consent rate, it will be feasible to enroll approximately 55 subjects over 6-12 months. Our final anticipated sample size will be 50 subjects after accounting for an estimated 10% dropout rate prior to completing 24 weeks of follow-up. Ten of these subjects will be autologous HCT candidates. Forty will be allogeneic HCT candidates, of which five will be cord blood HCT candidates. Given our sample size, we will be able to estimate a half-life for VIR-7831.

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1. BACKGROUND

Respiratory infections after hematopoietic cell transplantation (HCT) lead to significant morbidity, mortality, and health care costs. Early after transplantation, HCT patients have incomplete humoral immunity, making them extremely vulnerable to infections. Up to a third of HCT recipients acquire a respiratory viral infection within six months of transplant(1-7). In up to a third of those patients, the virus progresses from the upper to the lower respiratory tract (LRT)(2, 5). Once the virus gains a foothold in the lower tract, little can be done for most viruses beyond supportive care. As a result, up to 40% of patients with lower tract disease die within three months. The newly emerged COVID-19 pandemic caused by SARS-CoV-2 poses a threat to HCT recipients and development of COVID-19 post-transplant is associated with poor overall survival(8-10). This virus has spread throughout the world at an alarming pace, leading to over 150 million cases and 3.1 million deaths as of April 30, 2021 (Johns Hopkins COVID-19 dashboard).

mAbs can be used to prevent disease in vulnerable populations when given as prophylaxis. For example, the mAb palivizumab is approved as prophylaxis against pneumonia caused by respiratory syncytial virus and is administered to high-risk infants. Protective mAbs against SARS-CoV-2 are urgently being developed, but their role in providing long-term protection in the setting of HCT remains to be determined. mAbs against SARS-CoV-2 administered pre-transplant or early post-transplant represent a strategy to reduce the risk of COVID-19 among HCT recipients. Vir Biotechnology, Inc. (Vir) has developed a fully human neutralizing anti-SARS-CoV-2 antibody, VIR-7831 (GSK4182136), which contains a 2 amino acid Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life(11-13). VIR-7831 binds to a conserved epitope on the SARS-CoV and SARS-CoV-2 spike protein and has been shown to neutralize pseudovirus and live virus in several independent laboratories(14). VIR-7831 was granted Emergency Use Authorization by the Food and Drug Administration (FDA) in May 2021 for early treatment based on the interim analysis of the Phase 3 COMET-ICE clinical trial (NCT04545060). The COMET-ICE study population included adults with mild or moderate COVID-19 who were at high risk for progression to severe disease. On March 10, 2021, an independent data monitoring committee recommended that the trial be stopped for enrollment due to evidence of profound efficacy, demonstrating an 85% reduction in hospitalization or death when VIR-7831 was given early after infection as monotherapy. The multi-center, double-blind, placebo-controlled Phase 3 trial assessed the safety and efficacy of a single intravenous infusion of VIR-7831 (500 mg) or placebo in non-hospitalized participants globally, and this interim analysis included 291 patients in the treatment arm and 292 patients in the placebo arm. The primary efficacy endpoint was the proportion of patients who had progression of COVID-19 as defined by the need for hospitalization for at least 24 hours or death within 29 days of randomization.

The 500 mg dose of VIR-7831 has reduced *in vitro* neutralization potency against the Omicron BA.2 subvariant which has emerged as the predominant variant of SARS-CoV-2 in the United States. However, VIR-7831 retains protective efficacy *in vivo* due to its Fc effector functions(15). An increased dose of 2,000 mg is being proposed for the remainder of participants enrolled in this study to increase the expected duration of coverage given the current BA.2 predominant environment.Based on pseudotype and live virus neutralization data and pharmacokinetics (PK) data from multiple clinical studies evaluating the 500 mg dose, a preliminary population PK model was developed using data across several studies including COMET-TAIL, COMET-ICE, COMET-PEAK, BLAZE-4 and a PK study in individuals of Japanese and Caucasian descent. The predicted median (10th, 90th percentile) serum concentrations of sotrovimab at week 12 following a single 2000 mg IV dose is 84.3 (52.8,126.7) µg/mL. When assuming a lung:serum

ratio of 25%, a 2000 mg IV dose is expected to provide coverage against BA.1, BA.2 and BA.3 with serum concentrations achieving 13x, 1.4x and 5.6x lung tissue adjusted EC90 in 90% of patients at Week 12, respectively. When assuming a more conservative lung:serum ratio of 10%, a 2000 mg IV dose is expected to maintain serum levels at or above 5.3x, 0.56x, 2.23x lung tissue adjusted EC90 at Week 12 in 90% of patients for BA.1, BA.2 and BA.3 variants, respectively. Under the 10% and 25% lung:serum ratio assumptions, concentrations of sotrovimab at week 12 following a 2000 mg IV dose are expected to provide adequate protection in ≥90% of patients against variants that confer up to 20-fold and 49-fold shift in EC90 compared to WT, respectively. Similarly, this dose of sotrovimab at week 12 is expected to achieve adequate coverage for ≥50% of patients against variants that confer up to 31- and 78-fold shift in EC90 compared to WT when lung:serum ration are assumed to be 10% and 25%, respectively.

The normal serum half-life of immunoglobulin G (IgG) is approximately 21 days and is regulated by a balance of FcRn-mediated endocytosis and recycling versus endosomal degradation. To provide a product that has the potential to address multiple urgent medical needs including treatment, post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP), a molecule with extended half-life is preferred. The well-characterized LS modification (M428L and N435S) increases immunoglobulin G1 (IgG1) binding to FcRn only at the acidic pH of the endosomal compartment, thereby increasing recycling of IgG back into the circulation(11-13). Notably, the LS mutations do not affect binding to FcγRs or complement and thus do not impair Fc-mediated effector functions. Transcytosis of IgG across mucosal surfaces including respiratory epithelium has been shown to be FcRn dependent(16, 17), thus the LS modification allows for less frequent dosing, an important characteristic for a product intended to be used in the prophylaxis setting. Moreover, this characteristic of the LS modification may increase respiratory mucosal distribution, an important consideration in respiratory diseases.

The LS mutation has previously been studied in humans in the context of a mAb targeting the CD4 binding site of the HIV-1 envelope glycoprotein (VRC01LS; NCT0259989, NCT02797171). VRC01LS was reported to be safe and well tolerated at doses of 5 to 40 mg/kg IV and at 5 mg/kg subcutaneous in healthy volunteers(13). PK analysis showed a half-life of 71 days, more than 4-fold longer than that seen previously with the parental wild-type molecule. No anti-drug antibodies (ADAs) were detected out to 48 weeks(13). This molecule continues in clinical development for treatment of HIV infection in adults and children (NCT02256631, NCT03707977). Similarly, VIR-2482, a neutralizing mAb against influenza A, demonstrated a longer terminal elimination half-life (mean: approximately 27 days) compared to the wild-type molecule (mean: approximately 13 days) in cynomolgus monkeys. VIR-2482 is now in a phase 1/2 clinical study (NCT04033406) and has been administered to healthy volunteers at doses up to 1800 mg. Preliminary data indicate the compound has been generally well tolerated with no significant safety issues identified, including in a phase 2/3 clinical study (NCT04545060) of 583 patients. Based on available data, the preliminary half-life estimate for VIR-2482 is approximately 58 days in humans.

2. STUDY PURPOSE AND RATIONALE

HCT recipients are most vulnerable to infection during the early post-transplant period; however, active immunization against SARS-CoV-2 is thought to be ineffective during this period because all patients continue on immunosuppressive medications to prevent graft-versus-host disease (GVHD) and the immune system is not yet fully reconstituted(18, 19). In addition, most HCT recipients lose their immunity to various pathogens as soon as during the first months after transplant, irrespective of pre-transplant donor or recipient vaccinations. Current guidelines recommend considering vaccination at least three months

after transplant even though efficacy is unknown and may be sub-optimal. Passive immunization with monoclonal antibodies (mAbs) against SARS-CoV-2 administered pre-transplant represents a strategy to reduce the risk of COVID-19 among HCT recipients this the period of vulnerability when vaccination is not recommended or when vaccine responses may be sub-optimal.

This is a prospective, open-label phase 1 clinical trial that will enroll hematopoietic stem cell transplant candidates to receive the mAb VIR-7831 targeting SARS-CoV-2. The primary objective is to assess the pharmacokinetics of this extended half-life mAb post-transplant.

Previous studies have found that the half-life of CMV- and RSV-specific antibodies is 7-10 days in HCT recipients which is significantly less than the 21-day half-life of IgG in healthy adults(20-22). Although the mechanism of this accelerated decay is unclear, one possible explanation is increased antibody loss through graft versus host disease (GVHD)-related gut leakage which may be more common among recipients of mis-matched unrelated donor stem cell transplants. Monoclonal antibodies against SARS-CoV-2 administered pre-transplant represent a strategy to reduce the risk of COVID-19 among HCT recipients. This study will assess the pharmacokinetics of one such monoclonal antibody with regards to half- in the serum in both autologous and allogeneic transplant recipients. As an exploratory analysis, nasal antibodies may also be measured to determine the bioavailability of VIR-7831 in the nose since this is the portal of entry for infection by SARS-CoV-2.

The paired collection of blood by venipuncture and TASSO will also provide information about how antibody levels correlate between the two collection methods and if a correction factor needs to be applied to the TASSO results. Preliminary and published data suggest high concordance rates in antibody levels as measured from capillary blood versus venous blood samples(23, 24). This information will help determine the half-life of VIR-7831 when blood is self-collected by TASSO alone after day +100 post-transplant when patients are followed less closely by the transplant service.

Overall, a better understanding of the kinetics of antibody decay in the serum could help determine the utility of immunoprophylaxis in bridging this window of vulnerability among HCT recipients. If the half-life of mAbs like VIR-7831 is diminished in allogeneic transplant recipients, re-dosing may need to be considered in order to bridge the entire window of vulnerability to SARS-CoV-2 post-transplant. If the half-life of mAbs is not altered in autologous transplant recipients, redosing may not be needed in this population.

3. STUDY OBJECTIVES

3.1 Primary Objective

To determine the levels of VIR-7831 mAb post-transplant in serum over time.

3.2 Secondary Objectives

1. To compare the half-life of VIR-7831 in autologous vs. allogeneic transplant, cord vs. non-cord allogeneic transplant, matched vs mis-matched donors, in patients with and without GVHD, and in patients with and without diarrhea

2. To monitor the frequency of breakthrough SARS-CoV-2 acquisition in HCT recipients who have received VIR-7831

3. To compare antibody levels from serum collected by venipuncture versus self-collected using a TASSO device.

4. To monitor the development of anti-drug antibodies

5. To monitor safety

6. Exploratory: To measure VIR-7831 and SARS-CoV-2 neutralizing antibodies in nasal swabs and SARS-CoV-2 neutralizing antibodies in serum.

3.3 Projected Target Accrual

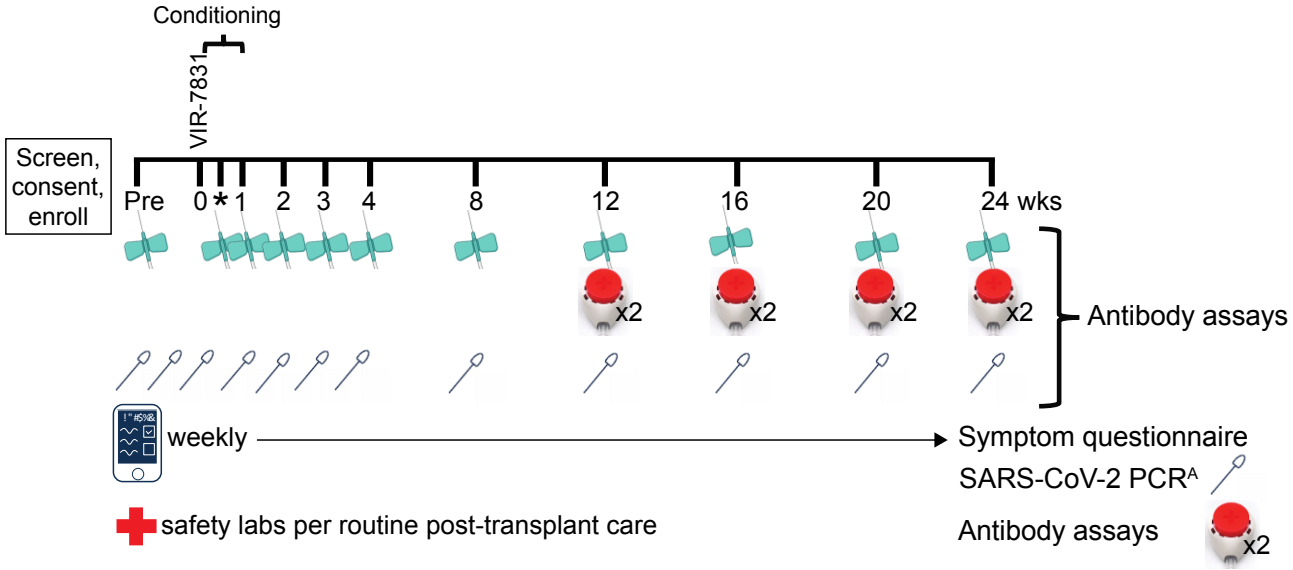
Table 1: Targeted / Expected Enrollment: HCT candidates			
Ethnic Category	**Patient Numbers**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	19	29	48
Ethnic Category Total of All Subjects*	20	30	50
Racial Category			
American Indian / Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	18	27	45
More than One Race	0	1	1
Racial Categories: Total of All Subjects*	20	30	50

4. STUDY DESIGN AND INVESTIGATIONAL PLAN

This is a prospective, open-label, phase 1 clinical trial of a mAb administered intravenously to HCT candidates within seven days prior to the start of conditioning for transplant. The target enrollment for this trial is 50 HCT candidates. Twenty subjects have already been infused with a 500 mg dose. Thirty additional subjects will be infused with the 2,000 mg dose. The study is open to anyone regardless of gender or ethnicity.

4.1 Overall Study Design

Figure 1: Overview of study design and timeline.



Participants will be screened, consented, and enrolled prior to transplant. Clinical evaluation will occur immediately prior to mAb administration. Participants will complete a weekly symptom questionnaire prior to and weekly after mAb administration for a total 36 weeks. Safety assessments will be performed with routine labs as part of standard stem cell transplant care. mAb will be administered intravenously within seven days of the start of conditioning, and the mAb will be infused at least 24 hours prior to the start of conditioning, i.e. mAb infusion will occur within 1-7 days prior to conditioning). Immediately prior to mAb administration (Pre), at the end-of-infusion (* in the schematic), weekly up to week 4, monthly up to week 12, and at week 24 after mAb administration, blood will be collected by venipuncture or from a central venous catheter if one is available (10-20 mL per blood draw). At week 12, and monthly thereafter to the end of the primary end-point (week 24), blood will be self-collected using a TASSO device if the participant is unable to return for a venous blood draw. Each timepoint for blood collection will utilize two TASSO devices (or one TASSO+ device). If a participant can present in clinic or is in the hospital, blood collection by venipuncture or from a central venous catheter is permitted instead of using a TASSO device. Nasal specimens will be collected by mid-nasal foam swab at the same time-points as blood draws for antibody testing. Additional nasal swabs may also be collected off-schedule as needed based on reporting of respiratory symptoms on the weekly questionnaire, up to week 36. If positive for SARS-CoV-2, weekly nasal swabs will be obtained longitudinally for SARS-CoV-2 PCR until negative or until week 36. If a participant can present in clinic or is in the hospital, blood can be collected by venipuncture or from a central venous catheter instead of by a TASSO device. Routine nasal swabs collected as part of standard clinical care for SARS-CoV-2 surveillance by PCR post-transplant are not shown. At week 36 (not shown), participants will receive a follow-up phone call to assess for the development of antibody dependent enhancement if they had COVID-19.

4.2 Protocol Enrollment

Enrollment is expected to take approximately 6-12 months. The duration of a participant's involvement with the study is expected to be approximately 24 weeks for the primary end-point with a follow-up call at week 36 to assess for antibody dependent enhancement. The study will be introduced to HCT candidates during intake or at transplant arrival at which time interested participants can contact the study team to discuss participation and to schedule a screening visit.

5. STUDY POPULATION

5.1 Inclusion Criteria, HCT candidates

Participants must meet all the following criteria to be eligible for the study:

Informed Consent and Willingness to Participate

1) Patients (or legally authorized representative if applicable) must be capable of understanding and providing a written informed consent

Age Criteria

2) Patients must be at least 18 years of age, of any gender, race, or ethnicity.

Nature of Illness and Treatment Criteria

3) Patients must be undergoing HCT (any donor or stem cell source including autologous or cord blood)
4) History of prior transplants are permitted
5) History of COVID-19, history of vaccination for SARS-CoV-2, positive PCR of a respiratory specimen for SARS-CoV-2 as long as it is not within four weeks from conditioning, or seropositivity for SARS-CoV-2 are permitted
6) History of SARS-CoV-2 infection or vaccination of the donor are permitted.
7) Post-enrollment vaccination is anticipated and permitted
8) Administration of IVIG before or during the study is permitted

5.2 Exclusion Criteria, HCT candidates

Participants who meet any of the following criteria will not be eligible for the study:

Other illnesses or conditions

1) Signs or symptoms of uncontrolled, active infection
2) Positive PCR result for SARS-CoV-2 within four weeks of scheduled conditioning
3) Pregnant or breastfeeding (this population is generally not cleared for transplant)
    - Pregnancy test is obtained as part of pre-transplant evaluation in women of child-bearing potential at arrival to transplant and again within 7 days of conditioning and will be confirmed as negative by review of the chart
4) Previous anaphylaxis or severe hypersensitivity reaction, including angioedema, to a mAb
5) Previous reaction to a mAb that required medical attention
6) Participants of other clinical studies that preclude the use of other investigational compounds
7) Participants who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol or unlikely to survive to the end of study

6. TREATMENT PLAN

6.1 VIR-7831 administration

VIR-7831 will be given intravenously as a single dose of 2,000 mg infused over approximately 60 minutes. A 500 mg single dose was used in the phase 3 COMET-ICE study and is the dose authorized under the EUA for early treatment. However, the 500 mg dose has reduced *in vitro* neutralization potency against the Omicron BA.2 subvariant which has emerged as the predominant variant of SARS-CoV-2 in the United States. An increased dose of 2,000 mg is predicted to rescue neutralization potency against Omicron BA.2 and will be used for the remaining 30 subjects in this study. A lead-in phase will consist of the first ten participants infused with the 2,000 mg dose. Lead-in phase participants will have a 120-minute post-infusion observation period, which is increased from the 60-minute monitoring period used for the previous 20 participants who received the 500 mg dose. If no infusion-related reactions (grade 3 or above) or serious adverse events are noted between 60-120 minutes post-infusion, the monitoring period may be shortened to 60 minutes. The mAb will be administered within seven days prior to the planned start of pre-transplant conditioning, and the mAb will be infused at least 24 hours prior to the start of conditioning, i.e. mAb infusion will occur within 1-7 days prior to conditioning). If conditioning is unexpectedly delayed by > 14 days after administration of VIR-7831, the subject can stay in the study but will not count towards the target sample size and will be excluded from the primary analysis. This would allow continued safety monitoring and analysis of secondary and exploratory objectives. Vials with the mAb will be stored between 2 and 8°C in the investigational drug service (IDS) pharmacy at FHCC.

6.1.1 Preparation of VIR-7831

VIR-7831 is manufactured in compliance with cGMP regulations. VIR-7831 is expressed in Chinese hamster ovary (CHO) cells using typical components for expression in mammalian cells. VIR-7831 drug product is provided as a sterile solution and contains no preservatives. Each single-use, 10 mL vial contains 500 mg of VIR-7831 (Gen2) at a concentration of 62.5 mg/mL as a clear liquid solution with a formulation of 20 mM histidine, 7% sucrose (w/v), 0.04% PS80 (w/v), 5 mM L-methionine at pH 6.0.

Product Storage:

The vials will be stored in the refrigerator at 2–8°C (35–46°F) at the IDS pharmacy and administered in the Infusion Services CTU. The mAb preparation does not contain preservatives and therefore should be used only once (no multiple entries into a vial).

6.1.2 Infusion Protocol

VIR-7831 is provided in a single-use vial in an individual carton and labeled as required per country requirement. Under normal conditions of handling and administration, study drug is not expected to pose significant safety risks to site staff, but adequate precautions should be taken to avoid direct eye or skin contact and the generation of aerosols or mists. Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. If evidence of such defects is observed, the product should not be used. Infusion will be performed either by inpatient nursing or by outpatient infusion center nursing.

1) The vial is equilibrated to room temperature for at least 15 minutes. Gently swirl the vial to mix without creating air bubbles. The IV solution can then be prepared using either empty or pre-filled sterile infusion bags as specified in the pharmacy manual.

2) Pre-infusion blood sample (approximately 10 mL) and nasal swab will be collected

3) After preparation of the injection site with an appropriate germicide, immediately inject the mAb intravenously. The mAb can be administered through a central line if the participant has one that is functional. The infusion duration is approximately 60 minutes.

6.1.3 Acute infusion reactions.

After injection, the first ten participants receiving the 2,000 mg dose will be observed for 120 minutes for any symptoms (none are expected). If there are no infusion-related reactions (grade 3 or above) or serious adverse events, the monitoring period for the next twenty participants can be shortened to 60 minutes. Participants will be encouraged to contact the investigator if there are any concerns of adverse events following the infusion. A physician, nurse, nurse practitioner, and/or physician's assistant will assess for initial infusion reactions and record solicited adverse events. IV infusion will be administered in the clinic with staff trained in emergency care & resuscitation procedures & emergency care kit on hand during treatment & post therapy observation periods. Vital signs will be monitored at the beginning and end of the 60-minute IV infusion. Subjects will be clinically observed for at least 60 minutes (120 minutes for the lead-in phase) post-infusion during the observation period. Vitals will be measured every hour during the observation period.

If a participant experiences a Grade 2 infusion-related reaction, nursing will be instructed to pause the infusion. The infusion may subsequently resume at a slower pace of infusion, at the investigator's or clinician's discretion, and/or after symptomatic treatment (e.g., antihistamines, IV fluids). Investigators and clinicians will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions. After infusion, study participants will be provided with investigators' contact information and asked to contact the study team if they experience subsequent adverse events, to collect unsolicited adverse events and SAEs.

Grading system from NCI CTCAE 5.0

Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated

Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death

7. POTENTIAL RISKS AND TOXICITY MONITORING

VIR-7831 has been administered in a Lead-In study phase (based on the 1:1 randomization scheme; overall N = 21) and was generally well tolerated as a single IV infusion at a dose of 500 mg. No subjects died or discontinued from the study due to adverse events (AEs). Based on safety assessment of unblinded Lead-In data, the Independent Data Monitoring Committee (IDMC) recommended initiation of the Expansion study phase. The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of VIR-7831 is primarily based on an interim analysis from 868 patients through Day 15. All patients received a single 500-mg infusion of VIR-7831 (N = 430) or placebo (N = 438). Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each. Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with VIR-7831 and 1% of patients treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate). One case of anaphylaxis was reported following VIR-7831 infusion in a study in hospitalized patients; the infusion was immediately discontinued, and the patient received epinephrine. The event resolved but recurred within 2 hours; the patient received another dose of epinephrine and improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following VIR-7831 infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. The most common treatment-emergent adverse events observed in the VIR-7831 treatment group in COMET-ICE were rash (2%) and diarrhea (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with VIR-7831 compared to placebo. The 250 mg and 500 mg IM doses were evaluated in COMET-TAIL (NCT04913675). So far, reported AEs were not found to be dose-dependent, suggesting a large increase in rate of AEs with 2000 mg IV of sotrovimab is unlikely. We will monitor all subjects for at least 60 minutes (120 minutes for lead-in participants) post-infusion.

Antibody-dependent enhancement of disease and anti-drug antibodies have not been observed *in vitro*, in animal models, or in clinical studies thus far with VIR-7831(25, 26). Participants will receive a phone call at week 36 to monitor for the development of antibody-dependent enhancement of disease. There is currently no available PK or immunogenicity data on a 2000 mg IV dose. Since sotrovimab exhibits dose proportional PK, exposures would be expected to be dose proportional between a 500 mg and 2000 mg IV doses. In the GLP repeat dose IV monkey toxicology study there were no toxicity findings at doses up to 500 mg/kg, the highest dose tested and the no-observed-adverse-effect-level (NOAEL). Assuming dose proportional increase in exposures at 2000 mg, sotrovimab C_{max} and area under the curve (AUC) in patients are expected to be 15.5 and 13.5-fold lower than C_{max} and AUC values from the toxicology study at the NOAEL, therefore, supporting the evaluation of sotrovimab at the higher clinical dose of 2000 mg IV. Sotrovimab is also considered low risk for immunogenicity based on intrinsic product characteristics (i.e., quality of GMP manufacturing controls and release specifications), extrinsic factors (i.e., administered as a single dose) and patient population (i.e., no apparent heightened risk of immune response). Limited preliminary analysis of immunogenicity data through Day 29 is available from 391 and 38 subjects given 500 mg IV in COMET-ICE and Japan-PK studies, respectively. To date, the incidence of treatment-emergent ADA responses has remained low, with no detectable impact on safety or efficacy. These clinical findings align with the low immunogenicity risk profile and the risk

prediction would not be expected to change substantially at higher doses when the product is administered as a single dose by the same route.

Drawing blood is a routine part of transplant care but can cause bleeding, bruising, pain, soreness, redness, swelling, itching, and/or muscle damage at the site where blood samples are taken. Rarely an infection at the site where blood samples are taken may occur or a blood clot may form. There is also the risk of fainting, dizziness, and anemia (low numbers of red blood cells).

Nasal swab sampling can result in discomfort or pressure during the procedure.

There may be risks of loss of privacy and confidentiality. All blood and swab samples will be given a code and stored securely.

7.1 Management of Toxicities

In the event of side effects attributed to the infusion or otherwise, patients should receive medical treatment as appropriate for the physiological abnormalities. Investigators and clinicians will be instructed to discontinue IV infusions for participants who develop Grade 3 or higher infusion reactions.

8. INFORMED CONSENT OF SUBJECT

Potentially eligible participants will be pre-screened and they or their legally authorized representative contacted to establish interest in the study. If interested, we will arrange a consent meeting in person during a video or phone call based on the preferences of the patient.

The key information about the purpose of the study, the procedures and experimental aspects of the study, the risks and discomforts, and alternative treatment will be presented to the participant. Participants will be given sufficient time to consider participation in the study. Participants will be asked to sign the consent prior to starting any study procedures. Consent from the patient will be obtained using forms approved by the Fred Hutchinson Cancer Center Institutional Research Board (FHCRC IRB). Once signed, a copy of the informed consent form will be given to the participant for their records. Participants may withdraw consent at any time throughout the course of the study. The rights and welfare of the subject will be protected by emphasizing to them that the quality of medical care will not be adversely affected if they decline/withdraw from the study.

Patients will initially be screened prior to their scheduled transplant. Enrollment will occur when data are reviewed for all inclusion and exclusion criteria by the study and the participant signs consent for infusion. A unique study number will be allocated to each patient and a log of enrolled patients will be maintained.

9. CLINICAL AND LABORATORY EVALUATIONS

A tabular schedule of events is provided in **Appendix A.** The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical or other factors.

9.1 Evaluations of enrolled patients

The consent and HIPAA authorization must be signed before any non-standard of care evaluations, including the first blood draw and nasal swab are performed. For patients who have consented, the following will be performed starting prior to infusion:

Questionnaires:

1) Participants will complete a weekly symptom questionnaire prior to mAb administration for a total 24 weeks. This questionnaire will be administered through a secure REDCap form and includes questions asking about eye, ear, nose, mouth/throat, sensory, chest, gastrointestinal, skin, muscle/joint, and general/constitutional symptoms. Participants that report one or more nose or chest symptoms will be asked to submit a blood and nasal swab specimen within 48 hours of symptom onset. This would allow for testing for SARS-CoV-2 infection by PCR.

Research samples:

1) Blood: All blood specimens are collected for the PK, neutralization, and IgG assays. Immediately prior to mAb administration, at the end-of-infusion, weekly up to week 4, monthly up to week 12, and at week 24 after mAb administration, blood will be collected by venipuncture (10-20 mL per blood draw). Blood drawn from a central venous catheter is permitted. Blood from venipuncture or a central venous catheter will be collected by inpatient nursing, outpatient nursing, phlebotomy, or the study team. If the participant is unable to return to the clinic or hospital for their last blood draw (week 24), we may provide a kit including blood collection tubes so a blood draw can be performed at the participant's local phlebotomy clinic or lab and shipped back to the study site. At week 12, and monthly thereafter to the last blood draw (week 24), blood will be by venous blood draw and self-collected using a TASSO-SST or TASSO+ device. The Tasso™ (Tasso Inc., Seattle WA) device is optimized for needle-free self-collection of blood at home. The TASSO-SST and TASSO+ devices can collect up to 300 µL and 600 µL, respectively, of whole blood from capillaries that can be spun down to serum. For each TASSO time-point, blood will be collected in either two TASSO-SST devices or one TASSO+ device. Each participant will be provided with a backup TASSO device for each TASSO collection time-point in case of device failure (expected 15% failure rate). We have experience using this technology with ongoing COVID-19 antibody testing studies at FHCRC (249 subjects and 2,289 devices). According to the manufacturer, the device has been used in over 5000 subjects since 2004 without any known severe events. The risk for participants is minimal and comparable to the procedures (lancing) for monitoring blood sugar levels. Additional blood may also be collected off-schedule as needed based on reporting of respiratory symptoms (one or more nose or chest symptoms) on the weekly questionnaire (if a specimen is not already scheduled to be collected within a week) for PK, neutralization, and IgG assays. Additional blood samples may also be requested due to inadequate collection or issues related to mail service delivery. Samples will be processed and stored at -20°C or -70°C until use, as appropriate.

2) Nasal specimens: Sample collection kits will be provided for the collection, handling, and shipping of samples to the Boeckh laboratory. Participants will self-collect mid-nasal swabs using a foam swab at the same time-points as blood draws. We have compared the performance of self-collected mid-nasal swabs to nasopharyngeal swabs collected by a medical professional and have observed high concordance (Table 2). In addition, we have found high concordance in the use of the mid-nasal foam swabs with nasal washes and flocked swabs for the detection of respiratory viruses (27, 28). Additional nasal swabs may also be collected off-schedule as needed based on reporting of respiratory symptoms (one or more nose or chest symptoms) on the weekly questionnaire within 48 hours of symptom onset, up to week 36. If positive for SARS-CoV-2, weekly nasal swabs will be obtained longitudinally for SARS-CoV-2 PCR until negative or until week 36. Samples will be processed and stored at -20°C or -70°C until use, as appropriate, for SARS-CoV-2 PCR testing and also potentially for antibody testing.

Table 2. Detection of SARS-CoV2 by PCR		Nasopharyngeal	
		Positive	Negative
Self-collected	Positive	36	0
	Negative	0	117
	Inconclusive	1	1

Samples collected in the inpatient unit or outpatient infusion center will be picked up by a member of the study team and brought to the Boeckh Lab on the same day of collection. Samples collected at home will be shipped overnight via FedEx to the Boeckh Lab.

Medical records:

Medical records from the University of Washington, outside health care providers, and databases maintained by the Fred Hutchinson Cancer Center will be reviewed for data such as subjects' demographics, underlying malignancy, treatment, and medical history with a focus on HCT related treatment and disease response.

- At screening, these include review of standard pre-transplant medical history and labs to assess inclusion/exclusion criteria:
    - Age
    - Underlying disease
    - HCT planned type and date
    - History of prior transplants

- History of COVID-19, positive PCR of a respiratory specimen for SARS-CoV-2 as long as it is not within four weeks from conditioning, or seropositivity for SARS-CoV-2
- History of SARS-CoV-2 infection or vaccination of the donor
- Ability to provide informed consent
- Prior administration of IVIG
- Pregnancy test results
- Previous known allergies to any component of VIR-7831
- Previous anaphylaxis or severe hypersensitivity reaction, including angioedema, to a mAb
- Participation in other clinical studies that preclude the use of other investigational compounds

- On the day of infusion, at the end-of-infusion, weekly to week 4, and monthly to week 24, these include review of the medical history with regards to underlying disease, medications, history of infections, history of vaccinations, and presence/severity of GVHD. In addition, standard post-transplant laboratory testing which are collected as follows from Day 0 to +100 post-transplant and as clinically indicated thereafter will be reviewed, including:
  - CBC daily until granulocytes > 500 cells/mm^3 and platelets > 20,000 cells/mm^3, then a CBC a minimum of once weekly until 100 days post-transplant.
  - Electrolytes, glucose, creatinine, BUN, every day as inpatient. At the ambulatory clinic, electrolytes are monitored a minimum of once per week.
  - Ca++, Mg++, PO4, albumin, twice a week as inpatient. At the ambulatory clinic, they are monitored a minimum of once per week
  - Bilirubin [total/direct], AST, alkaline phosphatase, LDH, a minimum of two times a week as inpatient. At the ambulatory clinic, monitoring is as follows: – If LFT's elevated: twice weekly.
  - INR is monitored weekly for patients on prophylactic Warfarin.
  - Blood cultures (aerobic and anaerobic) are obtained from patients receiving > 0.5 mg/kg/day of prednisone or prednisone equivalent. Twice weekly when inpatient.

9.2 Infusion Response Assessment

Bioanalytical PK method: This assay will be performed by Vir Biotechnology. A validated Electrochemiluminescence (ECL) Immunoassay is used to quantify sotrovimab in human serum samples. AbD34205 mu IgG2a (an anti-LS monoclonal antibody against the Fc region of VIR-7831) is coated onto an MSD High Bind plate (ECL capable). Sotrovimab in standards, QCs, controls and samples is captured onto the coated plate. After thorough washing of the wells to remove the unbound drug, Ruthenylated AbD42688 rFab is added to the wells. The conjugate binds to the captured sotrovimab. Following the incubation of the detection reagent, the plate is washed followed by addition of freshly prepared 1% formaldehyde for fixation and MSD read buffer. The assay plate is then read using an MSD ECL plate reader. Anti-drug antibodies may also be analyzed.

Neutralization assay: This assay may be performed at the Fred Hutch as an exploratory analysis using a SARS-CoV-2 pseudotyped virus assay as previously described(29). Briefly, this is a functional test to assess the ability of antibodies to bind and prevent infection of cultured cells with a pseudotyped virus that utilizes the spike protein of SARS-CoV-2 for infection and expressed luciferase. The endpoint neutralization titer of the serum will be determined as the dilution resulting in 50% neutralization (ID_{50}).

Binding antibodies (IgG): This assay will be conducted at the Fred Hutch. We will use an indirect enzyme-linked immunosorbent assay (ELISA) or Luminex assay for quantification of anti-SARS-CoV-2 spike and nucleoprotein IgG and total IgG as previously described(30). Briefly, 96-well microtiter plates will be coated with recombinant SARS-CoV-2 spike or nucleoprotein or polyclonal goat anti-human IgG. Serum samples will be initially diluted at 1:100 and nasal samples will be diluted 1:10. Diluted specimens will be incubated in duplicate on the plate followed by addition of secondary goat anti-human IgG-horseradish peroxidase (HRP). Optical densities (OD) will be measured with a spectrophotometer. Plates will include a positive control monoclonal antibody against SARS-CoV-2 spike. If available, donor serum may also be analyzed using an ELISA assay for SARS-CoV-2 spike and nucleocapsid protein to ascertain SARS-CoV-2 infection and vaccination status.

SARS-CoV-2 PCR: This assay will be performed by UW Virology. We will use the FDA-authorized Panther Fusion SARS-CoV-2 real-time RT-PCR assay to detect SARS-CoV-2 in nasal swabs. The limit of detection of this assay is 0.01 $TCID_{50}$/mL. The assay is a qualitative assay so does not have a lower limit of quantitation but does yield Ct values which will be recorded. The current standard practice for post-transplant care is to also obtain weekly surveillance PCR testing in allogeneic transplant patients prior to conditioning to day +100 post-transplant and also in autologous transplant patients prior to conditioning to day +30 post-transplant. These results will be obtained by review of electronic medical records. If the standard practice changes such that weekly surveillance swabs are no longer performed, we may provide additional swabs to participants for weekly PCR surveillance. A second foam swab will be performed as needed based on symptoms to test for acute SARS-CoV-2 infection. If positive for SARS-CoV-2, weekly nasal swabs will be obtained longitudinally for SARS-CoV-2 PCR until negative or until week 36. If breakthrough infection does occur, we will sequence the spike gene (or entire viral genome) to determine the variant and identify possible resistance mutations.

10. ADVERSE EVENT REPORTING

10.1 Definition of Adverse Events

Adverse Event: The International Council for Harmonization (ICH) guideline E6(R2) defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally related to the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews or by a mAb recipient presenting for medical care.

AEs must be graded by the Principal Investigator or an authorized designee for severity and relationship to study product (see below). Severity can be assessed by a licensed clinician (i.e., physician, nurse, nurse practitioner, physician's assistant). Relationship to study product can only be assessed by a clinician licensed to make medical diagnoses (i.e., physician, nurse practitioner, physician's assistant) listed on the Form FDA 1572.

Serious Adverse Event: An SAE is defined as an AE meeting one of the following conditions:

- Results in death during the period of protocol-defined surveillance, except deaths that are the result of trauma or accident or the primary underlying malignancy.
- Is life-threatening (defined as a subject at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization beyond the expected length of stay and during the period of protocol-defined surveillance. Hospitalizations for scheduled treatments, including scheduled admission for HCT are not SAE by these criteria.
- Results in a persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected Adverse Event: An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

10.2 Severity of Event

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 found at

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

10.3 Relationship to the Study Infusion

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications.
- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

10.4 Monitoring and Recording Adverse Events

Recording of adverse events will begin from the time of VIR-7831 infusion and continue to the end-of-study (week 36 follow-up call) for the participant. All SAEs will be followed through resolution or until return to baseline by a study physician.

Adverse events recorded in the appropriate case report forms include any SAE or Grade 2 or above Adverse Event. Information to be collected includes event description, date of onset, investigator assessment of severity, investigator assessment of relationship to study drug, date of resolution of the event, seriousness, and outcome. Any medical condition that is present at screening will be considered a baseline condition and will not be recorded as an AE unless there is worsening in the severity of the condition.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Adverse events will be assessed by the investigator or qualified designee. The investigator or relevant health care providers will attempt to establish a diagnosis of the event as indicated based on signs, symptoms and/or other clinical information. If the study team is informed of other unsolicited adverse events after the initial monitoring immediately after the infusion, evaluation will be similarly carried out.

10.4.1 Reporting Adverse Events

The sponsor-investigator assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32. The sponsor-investigator will be responsible for all communications with the FDA under the investigator's IND. Any correspondence to any government health authority regarding safety issues will be simultaneously copied to the drug-sponsor (Vir/GSK). The drug-sponsor will cross-report the relevant events to the VIR-7831 parent IND in accordance with 21 CFR312(c).

For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition described in 21 CRF 312.32 as an AE for which there is a reasonable possibility that the drug caused the adverse event where "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are serious, related, and unexpected will be reported to the FDA as an IND safety report, in accordance with regulations under 21 CFR 312.32.

SAEs as defined in Section 10.1 will be recorded on the appropriate SAE report form.

Reporting to FDA

- SAEs related to the study drug that are unexpected, and fatal or life-threatening will be reported to the FDA no later than 7 calendar days after SAE awareness.
- SAEs related to the study drug that are unexpected and serious (not fatal or life-threatening) are to be reported to the FDA no later than 15 calendar days after SAE awareness.
- All other SAEs will be submitted with the FDA Annual Report in summary form.

Reporting to GSK and Vir

- Any SAE, regardless of the causal relationship to Study Drug, occurring after the Subject has signed the Informed Consent Form through study end should be reported to the drug-sponsor (Vir/GSK) (safety mailbox provided below), no more than 24 hours after SAE awareness.
- All other events of special interest, including reports of pregnancy, abuse, misuse, medication error, overdose, and occupational exposure are to be captured using the SAE procedures but are to be considered as SAEs only if they meet serious criteria. All events of these types should be reported to Vir and GSK, regardless of whether or not there is an associated AE or SAE, no more than 24 hours after awareness.
  - If a pregnancy is reported during the study period, pregnancy information will be recorded and submitted to Vir/GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - The participant will be followed to determine the outcome of the pregnancy and for up to 1 year after birth. The investigator will collect follow-up information on the participant and the neonate/child and the information will be forwarded to Vir/GSK.
- Follow-up information to all initial reports will be sent to Vir and GSK no more than 24 hours after awareness.
- SAE reports and pregnancies shall be sent to GSK CMG via email at **OAX37649@gsk.com** or alternatively faxed to **+44(0)208 754 7822** if email is unavailable.

- Adverse Events of grade 2 or higher severity and Unexpected Adverse Events that are not attributable to the underlying disease for which HCT was performed, or not attributable to graft-versus-host disease (GVHD), not attributable to complications of immunosuppressive medications, and which is different from what is expected in the clinical course of a HCT recipient will also be reported to Vir Biotechnology at least annually.

Reporting to IRB: The investigator or designee must report events to the FHCRC IRB in accordance with the policies of the IRB.

- All problems, events (whether occurring on-site or off-site), or information which in the opinion of the investigator are unexpected, related, or possibly related to the research, and serious or suggest that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized must be reported to the IRB not later than ten (10) calendar days after he or she first becomes aware of it.
- All serious or continuing noncompliance with federal laws relating to research involving human subjects, or with the requirements or determinations of the IRB will be reported within ten (10) calendar days of discovery of the event.

11. STUDY WITHDRAWAL/DISCONTINUATION

Patients can withdraw from the study at any time point. Patients are also able to withdraw from study activities but still have safety outcomes recorded from review of the electronic medical record for safety purposes and to record safety outcomes. If conditioning is unexpectedly delayed by > 14 days after administration of VIR-7831, the subject can stay in the study but will not count towards the target sample size and will be excluded from the primary analysis. This would allow continued safety monitoring and analysis of secondary and exploratory objectives. Patients may also be discontinued from participating in the study at the Investigator's discretion.

12. STATISTICAL CONSIDERATIONS

12.1 Type of Study

This is a phase 1, prospective, open-label study to assess pharmacokinetics post-transplant of an extended half-life mAb targeting SARS-CoV-2.

12.1.1 Pharmacokinetics Assessment

- Primary objective: To determine the levels of VIR-7831 mAb post-transplant in serum over time. Both compartmental and non-compartmental analyses are used to assess pharmacokinetic parameters. The half-life of the anti-SARS-CoV-2 monoclonal antibody and neutralizing antibody titers in the serum will be calculated by a one-phase exponential decay model. We will compare fold-changes in antibody levels by normalizing to pre-transplant levels for each subject. Levels of VIR-7831 can be measured using an idiotypic antibody assay that is not affected by COVID-19 infection or vaccination. In addition, to half-life, we will calculate C_{max}, T_{max}, AUC from the concentration over time plots.

12.2 Secondary Objectives

- Secondary and exploratory objectives: We will compare antibody levels in autologous vs. allogeneic transplant, cord vs. non-cord allogeneic transplant, matched vs. mismatched transplants, in patients with and without GVHD, and in patients with and without diarrhea to test if HLA-mismatching, GVHD, and/or diarrhea are associated with accelerated antibody decay. Diarrhea will be assessed on the weekly questionnaire and the presence/severity/tissue involvement of GVHD will be assessed by review of the medical record at all timepoints indicated in Figure 1. We will also compare antibody levels from serum collected by venipuncture versus self-collected using a TASSO device and from fluid collected by nasal swabs. Based on preliminary and published data, we expect a high concordance between antibody levels from capillary blood collected by TASSO and venous blood collected by venipuncture or from a central venous catheter. If there is a slight discrepancy, we can calculate a correction factor based on the results from the paired specimens collected on week 12. If there is an unexpected significant discrepancy between antibody levels that cannot be corrected, we will have a venous blood draw at week 24 to calculate half-life using just venous blood samples. We will monitor for breakthrough SARS-CoV-2 infection by PCR of fluid collected by nasal swabs. If breakthrough infection does occur, we may sequence the spike gene (or entire viral genome) to determine the variant and identify possible resistance mutations. We will also measure anti-drug antibodies in case this is correlated with half-life. We will also monitor routine safety labs as part of standard post-transplant care. Comparisons will be tested using a t-test. As part of an exploratory analysis, we may also calculate the half-life of VIR-7831 and of SARS-CoV-2 neutralizing antibodies in nasal swabs and of SARS-CoV-2 neutralizing antibodies in serum after infusion of VIR-7831.

12.3 Sample Size and Accrual

At the Fred Hutch, we perform approximately 250 allogeneic transplants per year, approximately 5% of which involve umbilical cord blood donors. We also perform approximately 180 autologous transplants per year. The target enrollment for this trial is approximately 50 HCT candidates, of which ten participants will be autologous HCT candidates and 40 will be allogeneic HCT candidates (including cord blood HCT candidates). At least 8 of the allogeneic HCT candidates will be from HLA-mismatched (related or unrelated) HCT recipients. Based on the estimated number of treated patients per year (and previously treated patients since 2013), as well as the estimated number of patients that we may enroll (i.e., 'feasible' patients) after accounting for estimated eligibility and consent rates, it will be feasible to enroll approximately 55 subjects over 6-12 months. Our final estimated sample size will be 50 subjects after accounting for an estimated 10% dropout prior to completion of the full 24-week study period. If the dropout rate is higher at three months after mAb infusion, we may enroll more patients to achieve a target of 50 overall subjects. The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population. If accrual is slow, we may add another site. If accrual of the HLA-mismatched strata is slow, we may analyze and report the results in the HLA-matched strata once that is fully enrolled given the urgency of the pandemic.

- Primary objective: Our primary endpoint is to calculate the half-life of VIR-7831 post-transplant. Based on the half-life seen with other antibodies containing the LS mutation in adults who have not undergone transplant, we anticipate a half-life of up to 3 months. However, this half-life may be shortened in transplant recipients. Since we will use descriptive statistics, the sample size is

sufficient to provide data to calculate the half-life. Levels of VIR-7831 can be measured using an idiotypic antibody assay that is not affected by COVID-19 infection or vaccination.

- Secondary and exploratory objectives: We anticipate enrolling ten autologous HCT candidates. We anticipate enrolling approximately eight HCT candidates receiving HLA-mismatched (related or unrelated) transplants. This will serve as pilot data to examine whether HLA-mismatch affects the half-life of VIR-7831. To compare antibody levels between venipuncture vs TASSO and nasal swab in the first month of the study, we will have at least 4 x 50 = 200 specimens in each group. Based on the phase 3 COMET-ICE study, we do not anticipate any adverse effects or safety signals. Although there is currently no data available on the use of VIR-7831 as prophylaxis, it is possible we may observe breakthrough infection with SARS-CoV-2, particularly towards the end of the study as antibody levels wane.

13. DATA AND SAFETY MONITORING PLAN

13.1 Overall Scope of Monitoring Activities

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, the Principal Investigator will conduct continuous review of data and subject safety. FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

13.2 Monitoring the Progress of Trial and Safety of Participants

The first level of trial oversight for this protocol will be provided by the Principal Investigator and the Research Coordinator(s) who will provide continuous oversight of the trial. These individuals will meet at least weekly to review recently acquired data and adverse events. Serious adverse events will be reviewed upon occurrence to ensure prompt and accurate reporting to the appropriate committees and regulatory agencies as described above. The data recorded in the research charts and protocol database will be compared with the actual data available from the medical record and/or clinical histories. Data detailed in the research case report forms (CRFs) will include the nature and severity of reportable AEs. The Principal Investigator and all other study team members on the protocol have received formal training in the ethical conduct of human research. The study team will at monthly intervals provide GSK with a report detailing the progress of the study including study site initiation and study subject

recruitment. The study team will also keep GSK apprised of the progress ethics committee submissions, approvals, and amendments.

14. DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines for coding collection, key entry, and verification. Each subject is assigned a unique subject number to assure subject confidentiality. Information forwarded to regulatory agencies will refer to patients by a coded identifier and not by name. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Additional clinical data may be made available from the Fred Hutch core database which is managed and verified independent of the research group.

The research team will maintain Case Report Forms (CRFs) and associated research documentation for each patient treated under the protocol. This documentation includes both clinical data and study-specific documents for each patient. The Principal Investigator or a designee will verify completed CRFs against source documentation on an ongoing basis as they are completed for individual patients. Data required for analysis of patients treated on this protocol will be maintained in a password-protected study-specific database. Data from the CRFs are keyed directly into the database by authorized research staff and verified on an ongoing basis.

14.1 TERMINATION OF STUDY

Study accrual will terminate after the last participant has completed the final specimen collection described in this protocol. The study will continue until all samples are tested and the data is analyzed, which is expected to occur after approximately 2 years.

The PI may terminate the study at any time. The FDA, the IRB, or the US Office for Human Research Protections (OHRP) also have the authority to terminate the study should it be deemed necessary.

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APPENDIX A: Schedule of Events

		Day		Week																								
Assessment	Screening	0 (pre-infusion)[H]	0 (post-infusion)	1 (day 7±3)	2 (day 14±3)	3 (day 21±3)	4 (day 28±3)	5 (day 35±3)	6 (day 42±3)	7 (day 49±3)	8 (day 56±3)	9 (day 63±3)	10 (day 70±3)	11 (day 77±3)	12 (day 84±3)	13 (day 91±3)	14 (day 98±3)	15 (day 105±5)	16 (day 112±5)	17 (day 119±5)	18 (day 126±5)	19 (day 133±5)	20 (day 140±5)	21 (day 147±5)	22 (day 154±5)	23 (day 161±5)	24 (day 168±5)	36 (day 252±7)
I/E Criteria[A]	X																											
Informed consent/HIPAA[B]	X																											
PK sampling[C]			X	X	X	X	X				X				X				X				X				X	
ADA sampling[C]		X					X																				X	
Neutralizing antibody[C]		X	X	X	X	X	X				X				X				X				X				X	
TASSO[D]															X				X				X				X	
Nasal swab[E]		X	X	X	X	X	X				X				X				X				X				X	
Questionnaire[F]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[G]		X																										
VIR-7831 infusion		X																										

[A] Inclusion/Exclusion criteria will be assessed by the clinical research study coordinators
[B] Consent will be obtained by the PI, sub-investigators, or infectious disease advanced practice providers
[C] Blood draws by venipuncture or from a central venous catheter will be performed by nursing staff in the inpatient unit or by outpatient infusion center nursing. Phlebotomy can also be performed by trained and certified clinical study staff. The assays for PK, anti-drug antibodies (ADA), and/or neutralizing antibodies are performed at indicated time point where blood is collected by venipuncture and/or TASSO (day 0 pre-infusion and within one hour post-infusion and days 1, 7, 14, 21, 28, 56, 84, 112, 140, and 168).
[D] Three TASSO-SST or two TASSO+ devices will be provided for self-blood collection at each indicated time-point. Two TASSO-SST devices or one TASSO+ device with blood collected successfully will be sent to the Boeckh Lab. The extra device is in case of a device failure or for symptoms. If a participant can present in clinic or is in the hospital, blood can be collected by venipuncture or from a central venous catheter instead of by a TASSO device.
[E] Nasal swabs are self-collected for antibody testing. Additional nasal swabs may also be collected off-schedule as needed based on reporting of respiratory symptoms on the weekly questionnaire within 48 hours of symptom onset, up to week 36. If positive for SARS-CoV-2, weekly nasal swabs will be obtained longitudinally for SARS-CoV-2 PCR until negative or until week 36. Weekly nasal swabs collected as part of standard clinical care up to day +100 post-transplant for PCR surveillance of SARS-CoV-2 are not shown.
[F] Questionnaires are completed on a secure REDCap form available online.
[G] Blood pressure, heart rate, breathing rate, oxygen saturation, temperature collected prior to dose administration and at the end of the IV infusion of study drug and every hour during the observation period.
[H] Infusion will be performed either inpatient or in an outpatient infusion center with clinical staff present on the unit (either MD, advanced practice provider, or nursing staff).