DF/HCC Protocol #: **21-755**

TITLE: A Safety and Tolerability Study of Sotrovimab (VIR-7831) Prophylaxis Against COVID-19 Infection in Immunocompromised Individuals with Impaired SARS-CoV-2 Humoral Immunity

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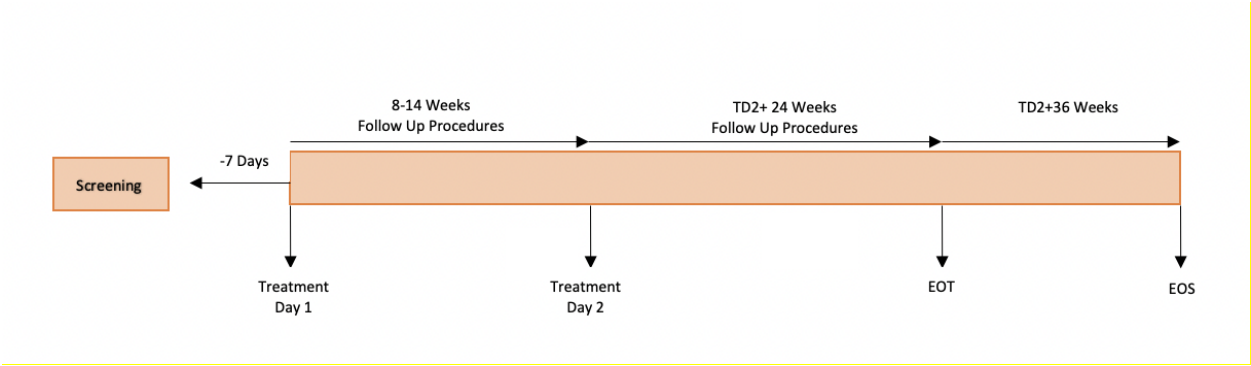
SCHEMA


8-14 Weeks
Follow Up Procedures
TD2+ 24 Weeks
Follow Up Procedures
TD2+36 Weeks
-7 Days
Screening
Treatment
Day 1
Treatment
Day 2
EOT
EOS

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1. OBJECTIVES

1.1 Study Design

This is an open-label study examining the safety and tolerability of sotrovimab, administered in two sequential doses as prophylaxis in immunocompromised patients with impaired humoral immunity against SARS-CoV-2. Approximately 93 patients will be enrolled in this study, 10 patients in an initial lead-in PK cohort initially planned to determine the optimal dosing interval between the first and second dose of sotrovimab and assess the safety and tolerability of the drug (prior to the spread of the BA.2 variant, which made it necessary to administer the repeat sotrovimab dose earlier than originally anticipated, using theoretical modeling and logistical considerations), 50 patients (including the 10 patients in the lead-in PK cohort) in a safety and tolerability lead-in cohort to examine rates of infusion-related reactions (IRR) with a 30-minute sotrovimab IV infusion, and the remainder in an expansion cohort for further assessment of the safety and tolerability of sotrovimab in this patient population, with the sotrovimab infusion duration determined by the rate of IRRs in the 50-patient safety and tolerability lead-in cohort. The first treatment consists of sotrovimab 500mg as an intravenous (IV) infusion over 30 minutes, followed by a one-hour monitoring period. The second treatment, to be administered in a time when BA.2 has become the dominant SARS-CoV-2 variant, will consist of sotrovimab 2000mg as an intravenous (IV) infusion over 60 minutes, followed by a two-hour monitoring period in the first 10 patients administered this dose, who will comprise a second lead-in safety cohort for this 2000mg dose, and a one-hour monitoring period in all patients subsequently receiving their second sotrovimab dose, as long as there are no grade >2 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in this 2000mg dose lead-in safety cohort.

1.2 Primary Objectives

- Assessment of the safety and tolerability of sotrovimab in immunocompromised patients with impaired humoral immunity against SARS-CoV-2, including:
    - The proportion of patients with treatment-emergent grade 3-4 adverse events (TEAEs).
    - The proportion of patients with treatment-emergent serious adverse events (SAEs).
    - The proportion of patients with adverse events of special interest (AESI), including infusion-related and hypersensitivity reactions, the development of anti-drug antibody (ADA) levels, and antibody-dependent enhancement (ADE) of COVID-19 disease.
- An assessment of the pharmacokinetics of sotrovimab in immunocompromised patients with impaired humoral immunity against SARS-CoV-2.

1.3 Secondary Objectives

- An assessment of rates of symptomatic COVID-19 infection (of any severity) in this cohort of immunocompromised patients with impaired humoral immunity against SARS-CoV-2 after receiving sotrovimab.
- An assessment of rates of asymptomatic COVID-19 infection in this cohort of immunocompromised patients with impaired humoral immunity against SARS-CoV-2 after receiving sotrovimab.
- An assessment of rates of severe COVID-19 infection (with hospitalization, intensive care unit admission and/or mechanical ventilation, or death), in this cohort of immunocompromised patients with impaired humoral immunity against SARS-CoV-2 after receiving sotrovimab.
- In patients who develop COVID-19, a determination of the greatest extent of COVID-19 symptoms using the 8-point National Institute of Allergy and Infectious Diseases ordinal scale (NIAID-OS), assessed at the end of hospitalization or 14 days after the diagnosis of COVID-19.
- An assessment of health-related quality of life measures longitudinally in participants over the course of the study using the SF-36 instrument.

1.4. Exploratory Objectives

- Assessment of rates of new cellular or antibody-mediated rejection events in SOT recipients exposed to sotrovimab.
- Assessment of rates of new-onset or worsening graft-versus-host disease in HCT recipients exposed to sotrovimab.
- Assessment of rates of new-onset allograft or stem cell failure requiring re-transplantation in HCT recipients exposed to sotrovimab.

BACKGROUND

2.1 Study Disease(s)

Summary of SARS-CoV-2 and an overview of the COVID-19 pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single stranded RNA betacoronavirus that can cause severe infections in humans, first identified in December 2019, and spreading widely across the globe since that time [1-3]. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020 [4]. As of September 2021, there have been over 4.7 million COVID-19-associated deaths worldwide [5].

Patients infected with SARS-CoV-2 have a wide range of clinical symptoms, from individuals who are fully asymptomatic to those with fulminant respiratory and multiorgan failure [6-7]. Many patients with COVID-19 experience a range of symptoms including fatigue, body aches,

fever or chills, sore throat, cough, shortness of breath, loss of taste or smell, headache, nausea, vomiting, or diarrhea [6-8]. Even when mild at onset, there is growing evidence these symptoms can persist for prolonged periods of time after the acute infection has resolved. Patients with severe SARS-CoV-2 infection often have dyspnea, hypoxemia requiring supplemental oxygen, pulmonary edema, lung infiltrates, and systemic inflammation, with elevated interleukin-6 and C-reactive protein levels [9-10]. Patients who become critically ill from COVID-19 infection and require intensive care and mechanical ventilation have high mortality rates [9].

Not all patients are similarly affected by COVID-19 infection - there is growing evidence that certain factors are associated with particularly severe clinical outcomes. Age is believed to be a strong risk factor for poor COVID-19 outcomes, and over 80% of COVID-19-related deaths have occurred in people who are 65 years or older [11]. Moreover, an array of pre-existing medical conditions have been linked to a high risk of severe disease and death due to COVID-19, including obesity and diabetes, chronic lung disease, hypertension, coronary artery disease, and underlying immunocompromising states, including both solid organ and stem cell transplants [12-13]. Finally, patients with many of these preexisting comorbidities have a significantly higher risk of in-hospital mortality [14,15].

For most patients, a full recovery from SARS-CoV-2 infection occurs 10-20 days after symptom onset [16]. However, infections can be severe and prolonged in immunocompromised patients, with a recovery period that can last for several months after infection, high associated mortality rates, and the selection of new SARS-CoV-2 variants in some of these patients [17-18].

SARS-CoV-2 Vaccine Responses in Immunocompromised Individuals

Many immunocompromised individuals have an impaired humoral immune response to SARS-CoV-2 vaccination compared to responses in the general population, especially patients receiving anti-CD20 antibodies, solid organ transplant recipients, patients with certain B-cell hematologic malignancies, and stem-cell transplant recipients, including CD-19+ chimeric-antigen receptor T (CAR-T) cell recipients [19-29]. Only 44-70% of patients exposed to anti-CD20 therapies, 73% of hematopoietic cell transplant recipients, and 14% of CD19-CAR-T cell recipients develop anti-SARS-CoV-2 spike protein antibodies after two doses of SARS-CoV-2 mRNA vaccination [19-23]. Patients with B-cell hematologic malignancies, such as mantle cell lymphoma (44%), marginal zone lymphoma (62%), chronic lymphocytic leukemia (37-64%), Waldenstrom's macroglobulinemia (74%), follicular lymphoma (78%), and diffuse large B-cell lymphoma (79%), also have significantly impaired humoral responses to SARS-CoV-2 mRNA vaccination, especially patients treated with anti-CD20 antibodies, steroids, venetoclax, or Bruton's tyrosine kinase inhibitors, but also patients who have not recently received chemotherapeutic agents [24-29].

Patients with solid organ transplantation also have impaired humoral immune responses to SARS-CoV-2 vaccination, with only 36-62% developing a measurable antibody response to 2-vaccine SARS-CoV-2 mRNA regimens, with particularly low humoral responses in older solid organ transplant recipients and patients exposed to antimetabolite drugs [30-34]. While a third 'booster' dose of mRNA vaccine increases immunogenicity of the SARS-CoV-2 mRNA vaccines, with a detectable serologic response rising from 40% after dose 2 to 68% following dose 3, a substantial subset of solid organ transplant patients still do not develop evidence of humoral immunity to SARS-CoV-2 [34-36].

Patients with rheumatologic diseases, particularly those receiving rituximab and other anti-CD20 therapies, and patients with congenital immunodeficiency syndromes also have impaired humoral immune responses to SARS-CoV-2 vaccination [37-39].

These patients are also at higher risk of developing severe COVID-19 disease [9-10]. Therefore, alternative approaches are needed to prevent SARS-CoV-2 infection and mitigate disease severity in these particularly vulnerable patients.

COVID-19 Variants

With over 240 million confirmed cases and nearly 5 million deaths worldwide due to COVID-19 to date [40], there has been an accelerated search for both preventive interventions such as vaccines and effective therapeutic agents, such as antivirals and monoclonal antibody therapies. Over the course of the COVID-19 pandemic, several SARS-CoV-2 variants, including Alpha (B.1.1.7), Beta (B.1.351, B.1.351.2, B.1.351.3), Delta (B.1.617.2, AY.1, AY.2, AY.3), and Gamma (P.1, P.1.1, P.1.2), have spread widely [17-18].

The Delta and Omicron (BA.1, BA.1.1, BA.2, and BA.3) variants are more infectious and spread more efficiently than earlier lineages of SARS-CoV-2 [17, 41-43]. Since December 2021, the Omicron lineage has become the dominant variant of SARS-CoV-2 globally, with its distinct sublineages, BA.1, BA.1+R346K, BA.2, BA.2 + H78Y, and BA.3, which share 21 mutations in the spike protein. BA.2 contains 8 additional unique mutations while BA.1 and BA.1+R346K contain 13 and 14 unique mutations, respectively [41]. Importantly, at least 15 of these mutations are located in the receptor-binding domain of the S-protein [42].

Mutations in the spike protein of new variants such as those described above **continue to drive** resistance to existing monoclonal antibody treatment and vaccines [43-44]. Because the S-protein is the binding site for many monoclonal antibodies and the target of existing SARS-CoV-2 vaccine products, there has been growing concern about the antiviral efficacy of these agents. Several recent studies have demonstrated reduced susceptibility of the BA.2 subvariant to Sotrovimab, although the extent to which its antiviral efficacy is affected has varied widely across studies [41-42]. Mutations in the spike protein of new variants could potentially continue to drive resistance to existing monoclonal antibody treatment and vaccines [42-43]. Prevention and treatment strategies need to evolve with sufficient rapidity to address the ongoing development of resistance in emerging SARS-CoV-2 variants.

Existing COVID-19 Treatments and Preventive Therapies

<u>COVID-19 Treatments</u>

Antiviral agents: There are three antiviral agents currently authorized for treatment of COVID-19 in the US. Veklury (remdesivir) is an intravenous (IV) antiviral drug that has been approved for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with COVID-19 requiring hospitalization [13]. In December 2021, ritonavir-boosted nirmatrelvir was issued an EUA for the treatment of patients with mild to moderate COVID-19

aged ≥12 years and weighing ≥40 kg who are within 5 days of symptom onset and considered at high-risk The EPIC-HR trial found that this drug reduced the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high-risk adults with COVID-19 [45]. This agent has become first-line therapy for many patients with mild to moderate COVID-19 in the United States. Finally, the MOVe-OUT trial of the novel oral antiviral drug molnupiravir found that it reduces the risk of hospitalization or death in non-hospitalized patients with mild to moderate COVID-19 disease by approximately 30% compared to placebo [46]. This therapy received FDA EUA on in December 2021 for the treatment of high-risk adults with mild to moderate COVID-19, within 5 days of symptom onset and for whom alternative antiviral therapies are not accessible or clinically appropriate.

Monoclonal antibodies: Multiple monoclonal antibody therapies have received U.S. Food and Drug Administration Emergency Use Authorization. The Regeneron REGEN-COV antibody cocktail of casirivimab and imdevimab was approved under EUA for the treatment of mild to moderate COVID-19 disease in adults and in pediatric patients (12 years of age or older weighing at least 40 kg), who have positive results of direct SARS-CoV-2 viral testing and are at high risk for progression to severe COVID-19 and for post-exposure prophylaxis (PEP), but this cocktail was later de-authorized due to its severely reduced antiviral efficacy against the Omicron variant [47].

In February 2021, the Eli Lilly monoclonal antibodies bamlanivimab and etesevimab received EUA for the treatment of adults and children with COVID-19 who are at risk for worsening disease progression and for PEP in patients who are not fully vaccinated or not expected to mount an adequate immune response to SARS-CoV-2 vaccination, but its distribution was also halted in light of severely reduced antiviral efficacy against emerging SARS-CoV-2 variants [48]. In May 2021, sotrovimab received EUA for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death [49-50]. In March 2022, the distribution of sotrovimab was paused due to the spread of the Omicron BA.2 variant, given the reduced antiviral susceptibility of this variant to sotrovimab. In February 2022, the antibody bebtelovimab received EUA for the treatment of non-hospitalized high-risk patients with mild to moderate COVID-19 [51]. Bebtelovimab appears to retain its activity against the Omicron variant of concern (VOC) and both its BA.1 and BA.2 subvariants [52].

Immune modulators: There are two immune modulators, baricitinib (Olumiant) and tocilizumab (Actemra), with FDA EUA for the treatment of COVID-19. Baricitinib is authorized for the treatment of COVID-19 in combination with Veklury in hospitalized adults and children (2 years or older) who are receiving corticosteroids and need supplemental oxygen, mechanical ventilation (non-invasive or invasive), or extracorporeal membrane oxygenation (ECMO) [48]. Actemra is authorized for use in the same patient population as baricitinib but it does not need to be administered in combination with Veklury [53].

<u>Prevention</u>

Vaccines: In August 2021, the Pfizer-BioNTech COVID-19 messenger RNA vaccine, also known as Comirnaty, was approved by the U.S. Food and Drug Administration [54]. The Moderna and Janssen COVID-19 vaccines also received FDA EUA, with the Moderna vaccine receiving FDA approval [55-56].

Monoclonal antibodies: In addition to these modes of prevention, AZD7442 is an antibody combination that was recently shown to be an effective form of COVID-19 pre-exposure prophylaxis in the PROVENT Phase III clinical trial [57]. AZD7442 leverages a proprietary half-life extension technology and may provide 12 months of protection from COVID-19. This monoclonal antibody is delivered by intramuscular (IM) injection.

2.2 IND Agent

Sotrovimab Background

S proteins on the surface of SARS-CoV-2 bind to ACE2 receptors in host tissues, allowing viral entry into host cells and viral RNA replication [56]. The ACE2 receptor is prone to mutations, leading to resistance to currently available monoclonal therapies. Sotrovimab is an investigational engineered monoclonal antibody that targets a highly conserved epitope on the spike glycoprotein of SARS-CoV-2. Using Xmab Fc technology, this antibody has a modification in its Fc region that increases its binding affinity to receptor FcRn in lysosomes in endothelial cells, rescuing these antibodies from degradation, prolonging its serum half-life, and potentially increasing its bioavailability in tissues such as the respiratory mucosa. Sotrovimab targets a highly conserved spike epitope, with amino acid conservation > 99.99% for all amino acids based on >2,100,000 available sequences. Variants at two positions, E340 and P337, resulted in significant EC_{50} shifts indicating reduced susceptibility to sotrovimab. E340 and P337 are 99.99% conserved among sequences in the GISAID database (16 July 2021). Sotrovimab neutralizes SARS-CoV-2 live virus and retains activity against alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2) and kappa (B.1.617.1) variant live virus. In vitro sotrovimab neutralizes and retains activity against the alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2). delta plus (AY.1/AY.2) epsilon (B.1.427/B.1.429), iota (B.1.526), kappa (B.1.617.1), lambda (C.37) and mu (B.1.621) variant viruses in the VSV/VeroE6 pseudotyped virus system; against omicron BA.2 and BA.3, there are fold changes of 15.7 and 7.3, respectively, in a pseudotyped virus system, and 35.1 against BA.2 live virus [44, 58-60].

Sotrovimab has been authorized for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are at high risk of progression to severe COVID-19, including hospitalization or death, under a U.S. Food and Drug Administration Emergency Use Authorization (EUA) [49-50], although starting March 25, 2022, it was no longer authorized in states and territories where the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% [61].

Drug Interactions

No formal interaction studies have been conducted with sotrovimab. Sotrovimab is neither renally excreted nor metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

In *in vitro* pharmacodynamic studies with remdesivir or bamlanivimab, sotrovimab showed additive virologic effect and no antagonism with either agent.

COVID-19 Monoclonal Antibody Efficacy Trial-Intent to Care Early (COMET-ICE) Interim Clinical Trial Results

COMET-ICE, a phase 3, randomized, placebo-controlled pivotal trial of sotrovimab for the treatment of non-hospitalized patients with symptomatic COVID-19 and at least one risk factor for disease progression, was stopped in March 2021 by an independent data monitoring committee because of profound efficacy. An interim analysis of this study showed an 85% risk reduction in disease progression leading to hospitalization or death in patients treated with a 500 mg single intravenous dose of sotrovimab, compared to placebo [49]. In this study, 3 patients in the sotrovimab treatment group (1% of the 291 patients randomized to this arm) developed disease progression leading to hospitalization or death, compared to 21 patients in the placebo group (7% of the 292 patients randomized to this arm). Adverse events were reported by 17% of patients in the sotrovimab group and 18% of those who received placebo, and serious adverse events (SAEs) were less common in patients receiving sotrovimab (2%) than in those receiving placebo (6%) [50]. Based on this interim analysis of the COMET-ICE trial, sotrovimab was granted a U.S. Food and Drug Administration Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death [49].

Safety Profile of Sotrovimab in Clinical Studies

As of August 18, 2021, 1843 participants have received sotrovimab administered intravenously (IV) or intramuscularly (IM) in Vir/GSK-sponsored clinical studies. As summarized in the sotrovimab **Investigator Brochure v3**, no safety concerns for sotrovimab have been identified in these clinical studies, and sotrovimab has been safe and well-tolerated.

Rationale for Dose Selection

A dose of 500 mg was selected for the study based on *in vitro* neutralization data, *in vitro* resistance data, and intravenous (IV) pharmacokinetic (PK) data from the COMET-ICE trial [49]. The 500 mg dose is being evaluated in ongoing and halted clinical studies; COMET-ICE [NCT04545060], ACTIV-3-TICO [NCT04501978], COMET-PEAK (NCT04779879), COMET-TAIL (NCT04913675), and Study 217653 (NCT04988152). Sotrovimab (500 mg, IV) was assessed in participants with COVID-19 in an early treatment study, VIR-7831-5001 (214367, also known as COMET-ICE [NCT04545060]), with the aim of preventing disease progression in non-hospitalized participants. For the first planned interim analysis, the Independent Data Monitoring Committee (IDMC) met on 10 March 2021 and reviewed data from 583 participants.

The IDMC recommended halting enrollment in the trial due to overwhelming efficacy, with an 85% reduction in the risk of hospitalization or death in the sotrovimab arm versus the placebo arm (primary endpoint) [49].

Sotrovimab neutralized SARS-CoV-2 live virus with an average EC_{90} value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL) (PC-7831-0105). In resistance analyses, no viral breakthrough was observed through 10 passages at fixed concentrations of antibody, indicating the potential for sotrovimab to have a high barrier to resistance (PC-7831-0109). Using an increasing concentration selection method to force resistance emergence, E340A was identified as a monoclonal antibody-resistant mutant (MARM) conferring a >100-fold reduction in susceptibility to sotrovimab. Notably, E340 is 99.9% conserved among available SARS-CoV-2 sequences. Due to the binary nature of the resistance selection results, a specific inhibitory quotient (IQ) was not informed by the resistance profiling.

Based on IV PK data from the lead-in and expansion phases of the COMET-ICE study, the mean serum concentration of sotrovimab following a single 500 mg IV dose is 40.3 µg/mL (N = 469) at Day 29. Based on the non-compartmental analysis of intensive PK data from the lead-in phase, the sotrovimab median (range) half-life is estimated to be 56.5 (42.4, 77.3) days.

A 500 mg IV dose was initially selected to ensure that sotrovimab concentrations in the lung are maintained at or above levels anticipated to be neutralizing for the duration of the treatment window [62-66]. *In vitro* live virus assays indicated that, compared to wild type EC_{90} (0.288 µg/mL), Omicron BA.1 and BA.2 confer a 3.5-fold and 35-fold shift in EC_{90}, respectively (PC-7831-0155). Based on the EC_{90} of BA.2 and accounting for the lung:serum ratio as 25%, an IV dose of 500 mg is expected to maintain serum levels above tissue-adjusted EC_{90} at day 15 for 90% of patients and day 34 for 50% of patients.

This study will assess two intravenous (IV) doses of sotrovimab, administered on Treatment Day 1 and on a second dosing day approximately 8-14 weeks after the first dose. The dosing interval to be determined based on PK modeling of the duration of efficacy of sotrovimab as antiviral prophylaxis against the Omicron BA.2 subvariant, and the availability of the higher 2000mg dose for administration in the study.

The exposure after 2000 mg IV was predicted using a preliminary population PK model that was developed using data across several studies including COMET-ICE, COMET-PEAK, BLAZE-4 and a PK study in individuals of Japanese and Caucasian descent. The predicted median (10th, 90th percentile) sotrovimab serum concentrations at 16 weeks following a second sotrovimab dose of 2000 mg IV given 8 week or 12 weeks after the first 500 mg IV dose are 69.2 (38.7, 109.4) µg/mL and 64.5 (38.0,105.2) µg/mL, respectively. Tissue-adjusted EC_{90} values were calculated using different assumptions for lung:serum ratio of 25%, 15% or 10% (based on literature reports for monoclonal antibodies in general, and were used to estimate coverage above tissue-adjusted EC_{90} following the second dose of sotrovimab 2000 mg IV [67-72].

When assuming a lung:serum ratio of 25%, a 2000 mg IV dose is expected to provide coverage against the Omicron BA.2 variant in 90% of patients for approximately 4 months when given 8-12 weeks after the first dose. With more conservative assumptions of a lung:serum ratio of 15%

and 10%, a 2000 mg IV dose given 8-12 weeks after the initial 500 mg IV dose is expected to provide adequate protection against BA.2 in 90% of patients for approximately 2 months.

2.3 Rationale

The primary medical approach to preventing COVID-19 currently is centered on several widely available vaccine products. In the United States, there are currently three COVID-19 vaccines available, the Pfizer-BioNTech, Moderna, and Johnson and Johnson/Janssen vaccines. Both Pfizer-BioNTech and Moderna are messenger RNA vaccines while the Johnson and Johnson/Janssen vaccine uses an adenovirus DNA vector. The Pfizer-BioNTech vaccine was 95% effective at preventing laboratory-confirmed SARS-CoV-2 viral infection, while the Moderna vaccine was about 94.1% effective. In comparison, a single dose of the Johnson and Johnson vaccine was 66.3% effective in preventing laboratory confirmed SARs-CoV-2 infection. Both the Pfizer-BioNTech COVID-19 and Moderna vaccine received full FDA approval in August 2021 and January 2022, respectively [6].

Only 44-70% of patients exposed to anti-CD20 therapies, 73% of hematopoietic cell transplant recipients, and 14% of CD19-CAR-T cell recipients, for example, develop SARS-CoV-2 spike protein antibodies after two doses of SARS-CoV-2 mRNA vaccination [7-11] Patients with B-cell hematologic malignancies, such as chronic lymphocytic leukemia (37-64%), follicular lymphoma (78%), and diffuse large B-cell lymphoma (79%), also have significantly impaired humoral responses to SARS-CoV-2 mRNA vaccination, especially patients treated with anti-CD20 antibodies, steroids, venetoclax, or Bruton's tyrosine kinase inhibitors, but also patients who have not recently received chemotherapeutic agents [12-15, 41]. Among two preliminary studies on solid organ transplant patients receiving immunosuppressive drugs the prevalence of SARS-CoV-2 spike antibodies was found to be between 20-40% after two doses of the vaccine [16-17], with similarly low prevalence of spike antibodies in patients with rheumatologic diseases receiving anti-CD20 therapies and other immunodeficiency syndromes with impaired humoral immune responses [18-20]. Finally, all these patient populations are also at higher risk of severe COVID-19 disease, highlighting the need for alternative approaches to prevent SARS-CoV-2 infection in these particularly vulnerable patients.

There are also several treatments for COVID-19 that are currently approved or under investigation, including remdesivir, dexamethasone, tocilizumab, and antivirals (e.g., remdesivir, molnupiravir); however, none of these therapies are currently being used for the prevention of COVID-19 disease. A monoclonal antibody product called AZD7442 showed evidence of efficacy for COVID-19 pre-exposure prophylaxis in the PROVENT Phase III clinical trial [57].

Monoclonal antibodies represent a highly specific and versatile alternative for COVID-19 prevention and treatment. Given that passive immunity is an instantly effective inducer of neutralization, opsonization, complement activation and antibody dependent cellular cytotoxicity and does not depend on recipients' immune response, it appears to be ideal for immunocompromised patients who fail to develop SARS-CoV-2 spike antibodies with current available vaccines and vaccination guidelines [64]. In May 2021, sotrovimab received U.S. Food and Administration Emergency Use Authorization for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization and death [49-50], although as of March 25, 2022, it is no longer

authorized for the treatment of mild-moderate COVID-19 in states and territories where the proportion of COVID-19 cases caused by the Omicron BA.2 variant exceeds 50% [61].

The primary objective of this study is to assess the safety and tolerability of sotrovimab, administered for the prevention of SARS-CoV-2 infection and COVID-19 disease, and to determine the pharmacokinetics of sotrovimab in these patients when administered at baseline and with a repeat dose. Immunocompromised individuals with a negative SARS-CoV-2 spike antibody remain at an exceptionally high risk of this infection and severe clinical outcomes if they become infected, and measures to prevent COVID-19 infection in these vulnerable patients are needed.

2.4 Correlative Studies Background

N/A

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

The study population will consist of immunocompromised adults who have evidence of impaired humoral immunity to SARS-CoV-2 based on SARS-CoV-2 spike antibody testing performed within 28 days of enrollment. This population is ideal for the study of sotrovimab as pre-exposure prevention, as these individuals are believed to have impaired immunological protection from prior infection or SARS-CoV-2 vaccination, and therefore at particularly high risk of acquiring this infection and developing severe disease manifestations.

3.1.1 Participant must be 18 years of age or older at the time of consent and weigh at least 40 kg. Children will be excluded from this study because dosing and adverse event data are limited for the use of sotrovimab in participants <18 years of age.

3.1.2 Participant must have one of the following immunocompromising conditions that increases their likelihood of having an impaired humoral immune response to SARS-CoV2, while also increasing their risk of being infected with SARS-CoV-2 and risk of progression to severe COVID-19:

- Exposure to an anti-CD20 monoclonal antibody (e.g. all formulations of rituximab, obinutuzumab, ofatumumab, ocrelizumab, ibritumomab, tositumomab) for a hematologic malignancy or an autoimmune/inflammatory disease in the 12-month period prior to consent.
- Allogeneic hematopoietic cell transplant ≥ 3 months and ≤ 1 year prior to consent; or allogeneic hematopoietic cell transplant >1 year prior to consent *plus* active graft-versus-host disease on systemic immunosuppressive therapy.
- Chimeric antigen receptor (CAR)-T cell therapy ≥ 4 weeks and ≤ 2 years prior to consent.

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), multiple myeloma, or Waldenström macroglobulinemia.
- Solid organ transplant recipient receiving immunosuppressive therapy.
- Congenital immunodeficiency syndrome (e.g. Wiskott-Aldrich syndrome, DiGeorge syndrome, common variable immunodeficiency).
- Patients with hematologic malignancy or autoimmune/inflammatory disease exposed to immunosuppressive medications specifically associated with a blunted humoral immune response to SARS-CoV-2 vaccination (e.g. mycophenolate mofetil, azathioprine, methotrexate, Bruton tyrosine kinase inhibitors, ruxolitinib, venetoclax, or corticosteroids (prednisone >20mg or equivalent daily for at least 14 days) in the 3-month period prior to consent.

3.1.3 Female participants must be:

a. Postmenopausal for at least 1 year;
b. Post-hysterectomy and/or post-bilateral oophorectomy;
c. Of childbearing potential, with a negative urine or serum human chorionic gonadotropin pregnancy test prior to each sotrovimab dose, and agree to use a highly effective method of birth control throughout the study period.

   Highly effective methods of birth control for purposes of this study include:

   i. Use of an established oral, injected, transdermal, intravaginal or implanted hormonal form of contraception associated with inhibition of ovulation.
   ii. Placement of an intrauterine device or intrauterine hormone-releasing system.
   iii. Male partner sterilization.
   iv. Bilateral tubal occlusion.
   v. Sexual abstinence (*excluding* periodic abstinence [e.g. calendar, ovulation, symptom-thermal, or post ovulation methods] and withdrawal).

The effects of sotrovimab on the developing human fetus are unknown. Pharmacological studies of sotrovimab have not been conducted in pregnant women and there is limited clinical experience using sotrovimab in women who are pregnant or breastfeeding. However, there is the potential for sotrovimab to cross the placental barrier and be present in breast milk; therefore, this therapy could theoretically be passed from mother to child during pregnancy or breastfeeding. For this reason, even though monoclonal antibodies are not known to be teratogenic, women of childbearing potential must agree to use a highly effective method of birth control from enrollment through the study follow-up period. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should

inform her treating physician immediately. The pregnancy will be followed and any safety issue observed will be reported.

3.1.4 Participants must have a negative or low-positive (<50 U/mL) SARS-CoV-2 spike antibody assay result within 28 days of consent.

3.2 Exclusion Criteria

3.2.1 Participants with an active SARS-CoV-2 infection, with a positive SARS-CoV-2 RT-PCR or antigen test result within 21 days prior to consent.

3.2.2 Participants with symptoms suggestive of SARS-CoV-2 infection.

3.2.3 Close contact (less than 6 feet away for a cumulative total of ≥ 15 minutes over a 24-hour period) with an individual with COVID-19 in the 14 days prior to consent.

3.2.4 Individuals who are pregnant or breastfeeding.

3.2.5 Participants who are receiving any other investigational agents.

3.2.6 Participants who, in the judgment of the investigator, are likely to have a life expectancy of less than one year.

3.2.7 Known hypersensitivity to any constituent present in sotrovimab or any other anti-SARS-CoV-2 monoclonal antibody product.

3.2.8 Active enrollment on another interventional research study of any agent for the treatment or prophylaxis of SARS-CoV-2 infection.

3.2.9 Exposure to any other anti-SARS-CoV-2 monoclonal antibody product for the treatment of COVID-19 in the prior 6 months.

3.2.10 Exposure to any other anti-SARS-CoV-2 monoclonal antibody product for prophylaxis against COVID-19 infection in the prior 12 months.

3.2.11 Receipt of a SARS-CoV-2 vaccine dose within the prior 28 days.

3.3 Inclusion of Women and Minorities

Individuals of all genders, races, and ethnic groups are eligible for this trial. Individuals with disabilities, at the extremes of weight, and those whose preferred language is not English will be included as study participants if they meet the inclusion and exclusion criteria outlined in **Sections 3.1** and **3.2**.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1.Treatment Regimen

This open-label study of sotrovimab, administered as a 500mg intravenous (IV) dose at the start of the study (Treatment Day 1) and as a 2000mg intravenous (IV) dose at a second time point 8-14 weeks after the first dose (Treatment Day 2), determined by PK modeling of the duration of efficacy of sotrovimab as antiviral prophylaxis against Omicron BA.2 subvariant, and the availability of the higher 2000 mg dose for administration in the study, will provide an assessment of the safety and tolerability of this monoclonal antibody as a preventive approach to COVID-19 in immunocompromised individuals with impaired humoral immunity to SARS-CoV-2.

The first treatment consists of sotrovimab 500mg as an intravenous (IV) infusion over 30 minutes followed by a one-hour monitoring period. The second treatment, to be administered in a time when BA.2 has become the dominant SARS-CoV-2 variant, will consist of sotrovimab 2000mg as an intravenous (IV) infusion over 60 minutes, followed by a two-hour monitoring period in the first 10 patients administered this dose, who will comprise a lead-in safety cohort for this 2000mg dose, and a one-hour monitoring period in all patients subsequently receiving their second sotrovimab dose, as long as there are no grade >2 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in this 2000mg dose lead-in safety cohort. The infusion time will be 60 minutes for all patients receiving the repeat 2000mg dose.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Dose modifications are not allowed in this study.

Background Treatments

Patients may have received standard of care therapies for the prevention of SARS-CoV-2 infection prior to enrollment in this study, including any SARS-CoV-2 vaccines that are approved or available under Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration.

Rescue Treatments

If study subjects develop COVID-19, they may receive rescue treatment for COVID-19 per the local standard of care. If study subjects are exposed to a contact with active COVID-19, they may receive post-exposure prophylaxis (PEP) as per the local standard of care. If study subjects develop COVID-19 or receive post-exposure prophylaxis after the first sotrovimab dose but prior to receiving their second sotrovimab dose, they will not receive the second dose of sotrovimab. Completion of the study and other study assessments will be performed according to the study schedule. These rescue treatments will not be provided as part of the study.

5.2. Pre-Treatment Criteria

The screening period is the window between day -7 (7 days prior to Treatment Day 1) and Treatment Day 1. The purpose of the screening period is to assess the eligibility of study subjects to participate in this study.

Screening procedures include:

- Confirmation that the potential study subject meets the inclusion and exclusion criteria outlined in **Sections 3.1** and **3.2**.
- Participants must have a negative or low-positive (<50 U/mL) SARS-CoV-2 spike antibody test result within 28 days of consent, using an assay available under U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA). Potential study subjects who have not yet had SARS-CoV-2 spike antibody testing in this window should have a SARS-CoV-2 spike antibody test available under FDA EUA checked, such as the

Roche Elecsys Anti-SARS-CoV-2 S assay, both for routine clinical care and to help evaluate their eligibility for this study.

If the study subject meets inclusion and exclusion criteria, screening and Treatment Day 1 procedures may be performed on the same day. Informed consent should be completed during the screening visit.

Potential study participants need to meet all eligibility criteria outlined in **Section 3.1** and **3.2** prior to receiving their first dose of sotrovimab.

5.3.Agent Administration

Study subjects will receive sotrovimab 500mg as an intravenous (IV) infusion over 30 minutes on Treatment Day 1 and 2000mg as an intravenous (IV) infusion over 60 minutes on Treatment Day 2. Study subjects will be monitored for one hour after the end of each 500mg infusion. After receiving the 2000mg dose on Treatment Day 2, which will occur 8-14 weeks after the first dose, the first 10 patients administered this dose, who will comprise a lead-in safety cohort for this 2000mg dose, will be observed for a 2-hour monitoring period. Subsequent patients receiving this 2000mg dose will have a one-hour monitoring period following their dose, as long as there are no grade 3 or 4 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in the 2000mg dose lead-in safety cohort. If there are any grade 3 or 4 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in this cohort, infusion time may be extended beyond 60 minutes, and the monitoring time may be maintained at 2 hours following this dose for subsequent patients.

Sotrovimab is not a vesicant or irritant.

Vital signs (including body temperature, heart rate, blood pressure, oxygen saturation (SpO_2), and respiratory rate) will be collected according to the schedule outlined in **Section 10** (Study Calendar), including prior to and following sotrovimab dosing on Treatment Day 1 and the Treatment Day 2. Vital signs should be obtained after 5 minutes of rest (supine or sitting). Vitals signs that are obtained following each sotrovimab dose should be obtained **within 30 minutes** after drug administration has been completed.

An **electrocardiogram** (ECG) will be obtained according to the schedule outlined in **Section 10** (Study Calendar), including prior to each dose of sotrovimab.

Serum sotrovimab levels will be measured for PK assessment according to the schedule outlined in **Section 10** (Study Calendar), including prior to the second dose of sotrovimab on Treatment Day 2 and **within 1 hour** after each sotrovimab dose.

Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if needed during the infusion of study drug. **Infusion-related reactions** are

defined as any relevant adverse events occurring **during the infusion and up to 24 hours after** the infusion.

All **infusion-related reactions** and **hypersensitivity reactions** must be reported as adverse events of special interest (AESIs).

Pre-medications should not be given routinely prior to the first dose of sotrovimab. If an infusion-related reaction occurs during the first dose of sotrovimab that is not severe enough to warrant discontinuation of the study treatment for a participant, the study team may decide to administer pre-medications prior to the second sotrovimab dose for that participant, administering an oral antihistamine agent (e.g. diphenhydramine, loratadine, famotidine) at least 30 minutes prior to starting the second sotrovimab dose or an intravenous antihistamine agent at least 5 minutes prior to starting the second sotrovimab dose.

Management of Local Infusion Site Reactions

Patients may develop local infusion site reactions, including erythema, soreness, pruritus, or bleeding, which should be managed according to the table below:

Table 1: **Management of Local Injection/Infusion Site Reactions**

Signs and Symptoms	**Management**
Redness, soreness or swelling at the injection site	Apply a cold compress to the injection site(s) Consider giving an analgesic (e.g., ibuprofen, acetaminophen, paracetamol)
Itching and redness	Consider giving an anti-pruritic (e.g., diphenhydramine) Observe patient closely for the development of generalized symptoms
Slight bleeding	Apply pressure and an adhesive compress
Continuous bleeding	Place gauze pads over the site and maintain direct and firm pressure

Recognizing Systemic Reactions or Anaphylaxis

As with any monoclonal antibody therapy, hypersensitivity reactions to sotrovimab are possible. In the COMET-ICE pivotal trial, all hypersensitivity reactions were non-serious, of Grade 1 (mild) or Grade 2 (moderate) severity and reported in 2% of participants who received sotrovimab and in <1% who received placebo (9 participants treated with sotrovimab and 5 participants treated with placebo) [48]. None of the reactions in either arm led to pausing or

discontinuation of the infusions. No anaphylaxis events were reported in the COMET-ICE study in participants with mild to moderate COVID-19 not requiring hospitalization at study entry.

A potentially life-threatening allergic reaction (anaphylaxis) was observed in one adult participant who received sotrovimab in a study of individuals hospitalized with COVID-19 (the ACTIV-3 TICO study). The anaphylaxis was considered by the investigator to be related to study treatment. The participant was treated for the allergic reaction and recovered. Another patient who received sotrovimab under an emergency expanded access basis developed anaphylaxis shortly after the start of infusion and required hospitalization. No further details were provided.

Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Interruption of the Intravenous Infusion

The infusion should be paused if any of the following adverse events occur at **grade ≤ 2** (mild or moderate) severity, as defined in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 [73]:

- Sustained coughing
- Rash or pruritus
- Chills/Rigors
- Urticaria
- Diaphoresis/Flushing
- Hypotension
- Dyspnea
- Vomiting

These reactions should be treated symptomatically (e.g. antihistamines, IV fluids), and the infusion may subsequently resume at 50% of the original rate at the investigator's discretion when symptoms of these adverse events improve to ≤ grade 1.

If investigators feel there is a medical need to interrupt or discontinue the infusion for any reasons other than those listed above, they should use their clinical judgment in responding to these potential infusion-related reactions.

Termination of the Intravenous Infusion

The infusion should be terminated and **not restarted** if any of the following **grade 3 or 4** adverse events occur, as per DAIDS grading criteria [73]. In addition, if any of these **grade 3 or 4** AEs occurred with the first dose, the subject **should not receive the second dose**, but should continue all other follow-up through end of study visit.

- **Anaphylaxis**: The most common signs and symptoms of anaphylaxis are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10-20%

of patients have no skin findings. Anaphylaxis should be considered if the study subject develops the acute onset of an illness with skin and/or mucosal tissue involvement (e.g. **urticaria, lip swelling, tongue/uvula swelling, or pruritus**) with at least one of the following:

- Respiratory compromise (dyspnea, stridor, wheezing, bronchospasm, hypoxemia)
- Hypotension or associated symptoms suggestive of end-organ dysfunction (e.g. syncope, incontinence) [74].

- **Laryngeal or pharyngeal edema**
- **Chest pain**
- **Seizure**
- **Persistent, symptomatic hypotension** (defined as a systolic blood pressure (SBP) < 90mmHg with symptoms consistent with hypotension (e.g. lightheadedness, syncope) that persists despite reducing the infusion rate)
- **Other neurologic symptoms** (confusion, loss of consciousness, paresthesia, paralysis)
- **Any other symptom or sign that warrants termination of the IV infusion**, according to the judgment of the investigator.

Management of Suspected Anaphylaxis

The following procedures should be followed in the event of a suspected anaphylactic reaction [75]:

1. Call for additional medical assistance; activate emergency medical services.
2. Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry
3. First-line treatment:
    a. Administer epinephrine (1.0 mg/ml) aqueous solution (1:1000 dilution) – 0.5 mg (0.5ml) IM in the anterolateral thigh **OR** if using an epinephrine auto-injector – use 0.3 mg IM into the anterolateral thigh.
    b. May be repeated every 5-15 minutes up to 3 times.
4. Optional treatment (antihistamine):
    Diphenhydramine 50 mg oral/IV/intramuscular (IM) **OR** Hydroxyzine 25 mg oral/IM.
5. Administer supplemental oxygen (8-10 L/minute) via facemask, as needed.
6. Normal saline rapid bolus – treat hypotension with rapid infusion of 1-2 liters IV.
7. Monitor the study subject until emergency medical services arrive.

5.4. General Concomitant Medication and Supportive Care Guidelines

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (**Section 3.2**), including active enrollment on another interventional research study of

any agent for the treatment or prophylaxis of SARS-CoV-2 infection, receipt of any other anti-SARS-CoV-2 monoclonal antibody product for the treatment of COVID-19 in the prior 6 months or for prophylaxis against COVID-19 in the prior 12 months, or receipt of a SARS-CoV-2 vaccine dose within the 28 days prior to consent or during the study period.

Patients who develop COVID-19 during the study follow-up period or have close contact with an individual who has COVID-19 and qualify for post-exposure prophylaxis may receive treatment per the local standard of care.

If patients are due for another dose of SARS-CoV-2 vaccination during the study period, patients may receive this dose any time after receiving sotrovimab, outside of the 2-week period before their second sotrovimab dose [76]. Patients may receive other available anti-SARS-CoV-2 monoclonal antibodies authorized for pre-exposure prophylaxis, such as tixagevimab/cilgavimab, ≥ 10 weeks after their 2000mg sotrovimab dose, as a 2000mg IV dose of sotrovimab will protect 50% of participants with a serum concentration above EC90 of BA.2 at 14.76 µg/mL for 10 weeks, assuming a lung:serum ratio at 15% and assuming 100% of SARS-CoV-2 infections are caused by the BA.2 variant at this time.

Patients may otherwise continue their normal regimen of medications and procedures.

Sotrovimab is neither renally excreted nor metabolized by cytochrome P450 (CYP) enzymes, and interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

5.5. Criteria for Taking a Participant Off Protocol Therapy

The study will last approximately 44-50 weeks (see **Section 10** for the schedule of study visits, assessments, and sample collection):

- **Screening window**: patients will have a screening period that lasts up to 7 days (Day -7 to Treatment Day 1).
- **Study period**: From Treatment Day 1 to the end of treatment visit, patients will be followed according to the schedule of in-person and remote study visits, assessments, and sample collection points as outlined in **Section 10**. 168 days after Treatment Day 2, patients will have an in-person end of treatment (EOT) visit for sample collection and assessments.
- **Final remote visit**: Patients will have a remote/telephone end of study (EOS) visit 36 weeks/252 days after their final dose of sotrovimab, which corresponds to approximately 5 half-lives of sotrovimab since the final dose.

Subjects may be **discontinued from the study drug** (but continue to follow study procedures) for any of the following reasons:

- Occurrence of an AE that, in the investigator's opinion, warrants discontinuation of the subject from receiving further study drug.
- Pregnancy or initiation of breastfeeding.

- Treatment with other monoclonal antibodies active against SARS-CoV-2 for post-exposure prophylaxis after having a household contact with COVID-19 or for treatment of COVID-19 prior to Treatment Day 2.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in source documents and in the eCRF.

Participants removed from protocol therapy prior to dose 2 of study drug for any of the reasons listed above will not receive a second dose of sotrovimab, but they will be asked to complete all other study assessments according to the study calendar (**Section 10**).

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6. Duration of Follow Up

Participants will be followed for 36 weeks after their second dose of sotrovimab (corresponding to approximately 5 half-lives of sotrovimab since the final dose) or death, whichever occurs first.

Participants removed from protocol therapy due to unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7. Criteria for Taking a Participant Off Study

Subjects may be **discontinued from the study** for any of the following reasons:

- Withdrawal of consent by the subject and/or the subject's legally authorized representative. Any patient has the right to withdraw from the study at any time, for any reason, and without repercussions. As excessive withdrawals might threaten the interpretability and generalizability of the results, withdrawal of patients should be avoided whenever possible.
- Loss to follow-up (every attempt should be made to contact the subject).
- Intercurrent illness that prevents further administration of treatment.
- Death.

Participants who are discontinued from the study will be asked to complete an early termination visit (with study procedures as per the Treatment Day 2 + 168 day/end of treatment visit) at the time of study discontinuation.

The reason for a subject's discontinuation of treatment or withdrawal from the study will be documented clearly in the source documents and in the eCRF. In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Study subjects will receive two doses of sotrovimab, on Treatment Day 1 and Treatment Day 2. Dose modifications for individual patients are not allowed.

Interruption of the Intravenous Infusion

The infusion should be paused if any of the following adverse events occur at **grade ≤ 2** (mild or moderate) severity, as defined in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 [73]:

- Sustained coughing
- Rash or pruritus
- Chills/Rigors
- Urticaria
- Diaphoresis/Flushing
- Hypotension
- Dyspnea
- Vomiting

These reactions should be treated symptomatically (e.g. antihistamines, IV fluids), and the infusion may subsequently resume at 50% of the original rate at the investigator's discretion when symptoms of these adverse events improve to ≤ grade 1.

If investigators feel there is a medical need to interrupt or discontinue the infusion for any reasons other than those listed above, they should use their clinical judgment in responding to these potential infusion-related reactions.

Termination of the Intravenous Infusion

The infusion should be terminated and **not restarted** if any of the following **grade 3 or 4** adverse events occur, as per DAIDS grading criteria [73]. In addition, if any of these **grade 3 or 4** AEs occurred with the first dose, the subject **should not receive the second dose**, but should continue all other follow-up through end of study visit.

- **Anaphylaxis**: The most common signs and symptoms of anaphylaxis are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10-20% of patients have no skin findings. Anaphylaxis should be considered if the study subject develops the acute onset of an illness with skin and/or mucosal tissue involvement (e.g. **urticaria, lip swelling, tongue/uvula swelling, or pruritus**) with at least one of the following:

    - Respiratory compromise (dyspnea, stridor, wheezing, bronchospasm, hypoxemia)
    - Hypotension or associated symptoms suggestive of end-organ dysfunction (e.g. syncope, incontinence) [74].

- **Laryngeal or pharyngeal edema**
- **Chest pain**
- **Seizure**
- **Persistent, symptomatic hypotension** (defined as a systolic blood pressure (SBP) < 90mmHg with symptoms consistent with hypotension (e.g. lightheadedness, syncope) that persists despite reducing the infusion rate)
- **Other neurologic symptoms** (confusion, loss of consciousness, paresthesia, paralysis)
- **Any other symptom or sign that warrants termination of the IV infusion**, according to the judgment of the investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (**Section 7.1**) and the characteristics of an observed AE (**Section 7.2**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

Following the first dose of sotrovimab on Treatment Day 1 and up to the end of study visit (36 weeks after Treatment Day 2), study investigators must promptly record and report all **treatment-emergent serious adverse events (SAEs), grade 2 unexpected and related treatment-emergent AEs, grade 3 or 4 treatment-emergent AEs (TEAEs)**. All **adverse events of special interest (AESIs)**, regardless of grade, must be reported.

These events may be directly observed, unsolicited (reported spontaneously by the patient), or solicited by questioning the study subject at each in-person and remote study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The assessment of SAEs, TEAEs, and AESIs will be conducted by the investigator or qualified sub-investigators to determine causality and severity.

Events should be:

- Clearly documented in the site's source documentation with the investigator's signature.
- Followed up proactively at subsequent visits or contacts until the SAE, grade 3-4 TEAE, or AESI has resolved, stabilized, are otherwise explained, or the participant is lost to follow-up.
- Preferably reported as a diagnosis term. When a diagnosis term is unavailable, a primary report with a sign or symptom as the AE term should be entered until the diagnosis becomes available.

Isolated abnormal laboratory results, vital signs, and other diagnostic results or findings should be reported as TEAEs if they fulfill reporting criteria for the study or require corrective treatment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization).

Adverse Event Definition

An **adverse event** (AE) is defined as an untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether it is or is not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention [77].

Events that meet the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention or intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Clinically significant changes in laboratory assessments.

Events that do **not** meet the definition of an AE include:

- "Lack of efficacy" or "failure of expected pharmacological action" *per se* will **not** be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

An **unsolicited AE** is one that was not solicited using a diary or form with pre-specified criteria. Unsolicited AEs are obtained either by asking a general question or unprompted by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to **contact the site as soon as possible** to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Serious Adverse Event Definition

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to the study drug (e.g., a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an adverse event that hypothetically might have caused death, had it been more severe.
- Requires inpatient **hospitalization** or **prolongation of existing hospitalization**. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Of note, hospitalization for *elective treatment of a pre-existing condition that did not worsen from baseline* is not considered an AE.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions). This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a **congenital anomaly/birth defect.**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (e.g. invasive or malignant cancers, intensive treatment in an emergency room or at home for

allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of intervention dependency or intervention abuse).

- Additional sponsor SAE: Hy's Law case: **ALT ≥ 3x upper limit of normal** (ULN) AND **total bilirubin ≥ 2xULN (>35% direct bilirubin)** OR **INR >1.5** must be reported as a SAE.
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Criteria for reporting SAEs (**Section 7.3**) must be followed for these events.

7.1. Expected Toxicities

7.1.1. Adverse Event List for Sotrovimab

Adverse Events of Special Interest in Study Subjects Receiving Sotrovimab

Adverse events of special interest (AESI) will be assessed from patient consent until the end of study visit (36 weeks after Treatment Day 2).

Adverse events of special interest are defined as relevant known toxicities of therapeutic monoclonal antibodies and will be monitored by the study team during the study, including:

- **Hypersensitivity reactions** or anaphylaxis. See **Section 5.3** for guidance on the management of suspected hypersensitivity reactions or anaphylaxis. Hypersensitivity reactions any time following sotrovimab dosing developed in 2% of patients who received sotrovimab and <1% who received placebo, with a rash developing in some of these patients and bronchospasm 12 days after the sotrovimab dose in a patient with pre-existing asthma; all events were considered non-serious and most were grade 1 in severity. There were no anaphylaxis events in COMET-ICE.

  A potentially life-threatening allergic reaction (anaphylaxis) was observed in one adult participant who received sotrovimab in the study of individuals hospitalized with COVID-19 (the ACTIV-3 TICO study), however. The anaphylaxis was considered by the investigator to be related to study treatment. The participant was treated for the allergic reaction and recovered. Another patient who received sotrovimab under an emergency expanded access basis developed anaphylaxis shortly after the start of infusion and required hospitalization. No further details were provided.
- **Infusion related reactions**. See **Section 5.3** for guidance on the management of suspected infusion-related reactions. Infusion-related reactions developed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo within 24 hours

of dosing in COMET-ICE. Events reported 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) and none led to treatment interruption or discontinuation.

- **Immunogenicity-related adverse events** (development of anti-drug antibodies (ADA)). Unwanted immunogenicity may lead to the production of ADA by the host, which may inactivate the therapeutic effects of the treatment and, in rare cases, induce adverse events.

  Immunogenicity will be characterized by an assessment of ADA titers according to the Study Calendar (**Section 10**) over the study period, at the baseline/Treatment Day 1 visit prior to the administration of the first sotrovimab dose, day 29, at the sotrovimab second dose visit prior to the administration of the second sotrovimab dose, day 29 after the second sotrovimab dose, and day 168 after the second sotrovimab dose (the EOT visit). The ADA response categories and titer categories are defined as follows:

  - **Negative**: Sample with a confirmed negative result.
  - **Positive**: Sample with a confirmed positive result.
  - **Treatment-induced:** Subject that develops ADA *de novo* following drug administration (baseline negative or missing).
  - **Treatment-boosted**: Subject with pre-existing ADA that are increased relative to baseline following drug administration (e.g titer ≥ 9x baseline titer).
  - **Transient ADA**: Subject with treatment-induced ADA detected at only one time point (excluding baseline and final visit) or subject with two or more time points that are separated by no more than 16 weeks between the first and last ADA positive samples (irrespective of any negative samples in between) and the last sample is ADA negative.
  - **Persistent ADA**: Subject with treatment-induced ADA detected at two or more time points where the first and last ADA positive samples (irrespective of any negative samples in between) are separated by 16 weeks or longer or Subject with treatment-induced ADA detected at the final time point.

- Adverse events potentially related to **antibody-dependent enhancement** (ADE) of COVID-19 infection.

  Antibody-dependent enhancement (ADE) of disease theoretically can occur by facilitating viral entry into host cells and enhancing viral replication in these cells, by increasing viral fusion with target host cells, enhancing viral replication in these cells, or by enhancing disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs. This study will include participant follow-up for a period of 5 sotrovimab half-lives to assess for the potential of enhanced disease in the context of waning sotrovimab levels, which

may manifest as an increased incidence of severe or prolonged disease in those who develop SARS-CoV-2 infection.

There will not be a placebo arm in this study, but patients who develop incident COVID-19 infection over the study follow-up period will be assessed for potential ADE, which may manifest as increased severity or duration of illness in patients temporally related to sotrovimab exposure.

All **infusion-related reactions** and **hypersensitivity reactions**, per DAIDS grading criteria, and suspected **ADE** in patients who develop COVID-19, must be reported as AESIs. These AESIs must be followed up proactively at subsequent visits or contacts until they have resolved, stabilized, are otherwise explained, or the participant is lost to follow-up. ADA will be assessed at the end of the study in serum samples collected over the study period.

7.2. Adverse Event Characteristics

Determining the Severity of Adverse Events

The severity of adverse events (including test findings classified as adverse events) will be graded for each AE using the current version of the DAIDS grading criteria [73]. All appropriate treatment areas should have access to a copy of the DAIDS grading scale; a copy can be downloaded from the National Institute of Allergy and Infectious Diseases at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Assessing the Causality of Adverse Events

The investigator must provide an assessment of causality, determining whether there is a reasonable possibility that the investigational drug caused the adverse event, based on evidence or facts, clinical judgement, and the following definitions:

- **Related**: the adverse event follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical, or other external factors **OR** the adverse event follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
    - **Definite** – the AE is **clearly related** to the study treatment.
    - **Probable** – the AE is **likely related** to the study treatment.
    - **Possible** – the AE **may be related** to the study treatment.
- **Not likely to be related**: the adverse event does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state, or other external factors.
    - **Unlikely** – the AE is **unlikely to be related** to the study treatment.
    - **Unrelated** – the AE is clearly **not related** to the study treatment.

The causality assessment must be made based on the available information and can be updated if new information becomes available. The investigator should consider the temporal relationship (time to AE onset vs. time drug was administered), nature of the reaction (immediate vs. long term), clinical and pathological features, concomitant medications, underlying disease, and past medical history of the patient, while assessing causality.

All treatment-emergent SAEs, grade 2 AEs that are both unexpected and thought to be related to the study treatment, treatment-emergent grade 3 or 4 AEs (TEAEs), and all adverse events of special interest (AESIs), regardless of grade, must be reported with:

- The investigator's assessment of the event's seriousness, severity, and causality in relation to the study drug.
- A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF.
- Specific or estimated dates of event onset, treatment, and resolution.

Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE eCRF and retained at each study site, and available upon request for review.

7.3. Adverse Event Reporting

7.3.1. In the event of an unanticipated problem or life-threatening complications, treating investigators must immediately notify the sponsor-investigator.

7.3.2. Investigators **must** report to the sponsor-investigator any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, within 30 days of the last dose of treatment on the local institutional SAE form, and for this study, through the end of study visit 36 weeks after the second dose of sotrovimab.

7.3.3. Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the Institutional Review Board (IRB) of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Table 2. DF/HCC Reportable Adverse Events (AEs)

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

Furthermore, **all adverse events of special interest** (AESIs) of any severity, as outlined in **Section 7.1.1**, should be reported to the sponsor-investigator within **24 hours** of the investigator's knowledge of the event (except for ADA, which will be assessed at the end of the study in serum samples collected over the study period).

Expedited reporting requirements for AEs occurring on studies under an IND are as outlined in the table below:

Table 3. Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor-investigator, IRB, and FDA within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported to the sponsor investigator within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

7.3.4. Protocol-Specific Adverse Event Reporting Exclusions

N/A

7.4. Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5. Reporting to Hospital Risk Management

Each site PI will report to their local Risk Management Office any participant safety reports, sentinel events, or unanticipated problems that require reporting per institutional policy. The sponsor-investigator will also report any events that merit communication with the IRB via email concurrently to GSK (within **24 hours** of the sponsor-investigator's knowledge of the event).

7.6. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the sponsor-investigator on the case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in **Section 7.1** and in the **Investigator Brochure v3**.

8.1. Sotrovimab

8.1.1. Description

Sotrovimab (VIR-7831, GSK4182136, Xevudy) is a dual action engineered human IgG1κ monoclonal anitibody derived from the parental monoclonal antibody S309, a potent neutralizing antibody that binds to a highly conserved epitope of the SARS-CoV and SARS-CoV-2 spike protein receptor binding domain. The amino acid sequence of the complementarity-determining regions of sotrovimab is identical to the parent molecule S309, with the exception of one amino acid modification (N55Q) introduced to aid antibody developability. The Fc domain of sotrovimab has been engineered to provide extended half-life through the introduction of the well-characterized LS modification (M438L and N444S), which extends antibody half-life and is also expected to enhance distribution to the respiratory mucosa. Sotrovimab has a molecular weight of 150 kDa.

Intensive lead-in PK data from the COMET-ICE trial indicates that sotrovimab has a median terminal half-life of 48.8 days.

Sotrovimab, as a monoclonal antibody, is degraded into small peptides and individual amino acids. The high molecular weight of sotrovimab (approximately 150 kDa) suggests that renal elimination of intact sotrovimab is unlikely to be of importance and the clearance of sotrovimab is predicted to be largely mediated by proteolysis.

No formal interaction studies have been conducted with sotrovimab. Sotrovimab is neither renally excreted nor metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely. In *in vitro* pharmacodynamic studies with remdesivir or bamlanivimab, sotrovimab showed additive virologic effect and no antagonism with either agent.

8.1.2. Form

Sotrovimab is supplied in single-dose vials containing 500mg of sotrovimab in a volume of 8mL (62.5 mg/mL). Sotrovimab is a clear, colorless or yellow to brown solution. Sotrovimab is manufactured in compliance with cGMP regulations by Vir Biotechnology, Inc.

8.1.3. Storage and Stability

Study drug will be stored at each site at 2°C to 8°C [36°F to 46°F]. Vials should be stored upright and protected from light. Vials should never be frozen.

Sotrovimab is preservative-free; therefore, once diluted, the infusion solution should be administered immediately. If immediate administration is not possible, the diluted solution of sotrovimab may be stored for **up to 4 hours** at room temperature (20°C to 25°C [68°F to 77°F]), with the infusion starting within 2 hours of removal from refrigeration and completing (including

flushing the line) within 4 hours of removal of the bag from refrigeration, or refrigerated **up to 24 hours** (2°C to 8°C [36°F to 46°F]).

8.1.4. Compatibility

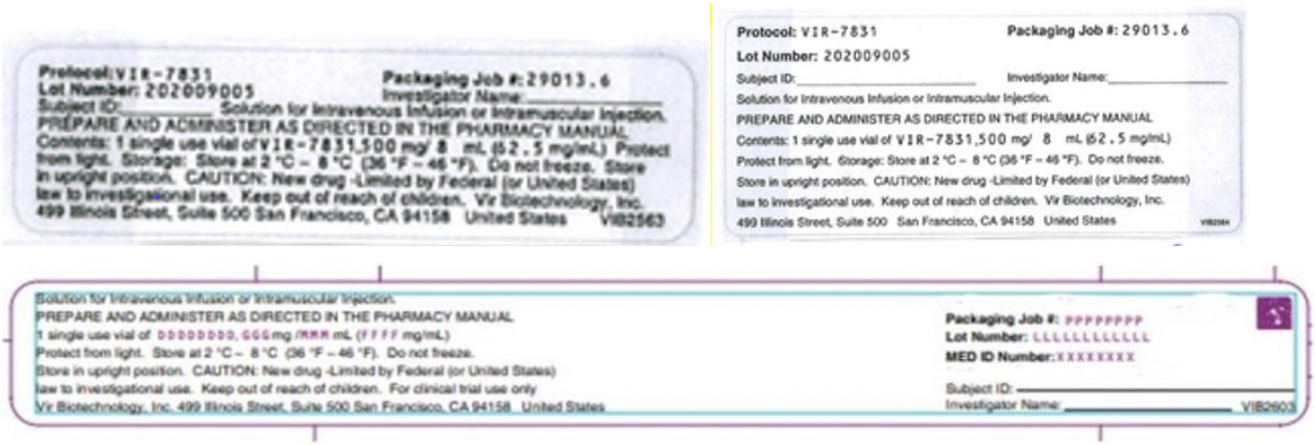
Sotrovimab must be diluted prior to intravenous (IV) administration in 0.9% sodium chloride, as outlined in **Section 8.1.7** below and in the **Pharmacy Manual**.

8.1.5. Handling

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique. 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.

8.1.6. Availability

Open label vials of Sotrovimab/VIR-7831 will be shipped from the study sponsor to the Investigational Drug Services (IDS) pharmacy at Brigham and Women's Hospital or the investigational pharmacy at Massachusetts General Hospital. For study patients enrolled and treated at Dana-Farber Cancer Institute, vials shipped to the IDS Pharmacy at Brigham and Women's Hospital will be transferred to the Dana-Farber Cancer Institute Pharmacy as needed via the inter-institutional drug transfer process. Each vial will contain 500mg of investigational drug in a volume of 8mL (62.5mg/mL). Vials will be labeled with a single panel label, with two types of clinical labeled stock available from supply (samples shown below).



8.1.7. Preparation

Sotrovimab must be diluted prior to intravenous (IV) administration, as outlined in **Section 3.4 of the Pharmacy Manual**.

Sotrovimab (VIR-7831) has been tested for compatibility with the materials listed below. Care should be taken to use equipment made from the materials listed when preparing and administering the doses.

Equipment required for IV administration of a 500mg dose:

- Pre-filled 50mL 0.9% saline infusion bags or empty 50mL infusion bags and bulk normal saline **OR** pre-filled 100mL 0.9% saline infusion bags or empty 100mL infusion bags and bulk normal saline
- Bag spike
- Venting dispensing pin
- 10mL**,** 30mL, and 50mL sterile syringes
- 0.2µm in-line filter (not required but recommended)
- 21-gauge stainless steel sterile needles
- Sterile infusion set
- Individual protective equipment
- Polypropylene Syringe
- Infusion pump for dosing (flow rate of 50 - 200mL/hr)
- Amber UV light-inhibiting (UVLI) sleeve to protect the study drug infusion bag from light during infusion.

Compatible materials:

A list of materials that have been shown to be compatible with Sotrovimab (VIR-7831) at a 500mg dose are:

- Polyvinylchloride (PVC) with and without DEHP
- Polyolefin (PO)
- Polycarbonate containers/syringes
- Ultra low density polyethylene
- Ethyl vinyl alcohol copolymer (EVOH, EVA)
- Silicone tubing
- Polyvinylidene fluoride (PVDF) filter materials
- Polyethersulfone (PES) filter materials
- Type I Glass

If available, it is recommended to use a laminar flow hood for dose solution preparations. Infusions must be prepared aseptically by the pharmacist/designated site staff. Aseptic technique must be strictly observed throughout the preparation process.

Preparation of Each Sotrovimab (VIR-7831) Dose (500mg):

1. Complete the infusion bag label for VIR-7831 with the following information using a permanent black marker:

    a. Participant study ID number

b. Site number where the infusion will be administered.

2. Remove one (1) vial of study drug from refrigeration. Allow the vial to **equilibrate** to ambient room temperature, protected from light, for at least **15 minutes**.

3. Visually inspect the vial for 5 seconds to ensure it is free from particulate matter and that there is no visible damage to the vial.

4. Gently swirl the vial several times before use without creating air bubbles.

    a. **Do not shake or vigorously agitate the vial**.
    b. If a vial is identified to be unusable:

        a. Take a photo of the damaged vial, if possible.
        b. Record details of the vial for accountability purposes.
        c. Retrieve a new vial and restart the preparation.
        d. Destroy the damaged vial per institutional policies and procedures.
        e. Follow the pharmacy procedure for updating study drug inventory.

5. The intravenous (IV) solution can be prepared using either empty sterile infusion bags or pre-filled infusion bags. There is an option to use either 50mL or 100mL infusion bags. (using aseptic precautions to prevent contamination).

Use of pre-filled, 50mL infusion bag:

- Using an appropriately sized fresh syringe and 21-ga needle, draw 8mL of normal saline from the infusion bag.
- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from the vial of study drug.
- Inject the 8mL of study drug into the infusion bag via the septum to bring the total volume to approximately 50mL.
- Record the time the vial was punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UV light-inhibiting (UVLI) sleeve).
- Discard any unused portion left inside the vial, as the product contains no preservative. The study drug inside the vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

Use of an empty sterile 50mL infusion bag:

- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from the vial of study drug.
- Inject the 8mL of study drug into the empty infusion bag via the septum.
- Using an appropriately sized fresh syringe and 21-ga needle, add 42mL of normal saline to the infusion bag via the septum to bring total volume to approximately 50mL.
- Record the time the vial was punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UVLI sleeve).
- Discard any unused portion left inside the vial, as the product contains no preservative. The study drug inside the vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

Use of pre-filled, 100mL infusion bag:

- Using an appropriately sized fresh syringe and 21-ga needle, draw 58mL of normal saline from the infusion bag.
- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from the vial of study drug.
- Inject the 8mL of study drug into the infusion bag via the septum to bring the total volume to approximately 50mL.
- Record the time the vial was punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UVLI sleeve).
- Discard any unused portion left inside the vial as the product contains no preservative. The study drug inside the vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

Use of an empty sterile 100mL infusion bag:

- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from the vial of study drug.
- Inject the 8mL of study drug into the empty infusion bag via the septum.
- Using an appropriately sized fresh syringe and 21-ga needle, add 42mL of normal saline to the infusion bag via the septum to bring total volume to approximately 50mL.
- Record the time the vial was punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UVLI sleeve).

- Discard any unused portion left inside the vial as the product contains no preservative. The study drug inside the vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

6. Complete the infusion bag label for Sotrovimab (VIR-7831) with the following information using a permanent black marker. At a minimum the labels should contain the following information:

STUDY 14210 OPEN-LABEL MEDICATION
Sotrovimab (VIR-7831)
Subject ID #: .....

Study Site #: .....
Visit #: .....
Date: .....
Lot #: …….....

Time when vial was punctured for intravenous infusion: .....
Time IV bag preparation complete: .....
Expiration time: .....
Prepared by: .....

7. Apply the infusion bag label to the infusion bag.

8. Details of dose preparation should be recorded on the **Dose Preparation Form** in the **Pharmacy Manual** or site equivalent. For each dose preparation, a new copy of this form is used to record the date, the participant number, the dosing day/week, the the number of vials used, the time of dose preparation, the expiration time and the name and signature of the person preparing the dose.

9. Attach an infusion set to the infusion bag. Follow institutional policy for the use of an in-line filter for administration.

10. Follow institutional procedures for priming the infusion set and programing the infusion pump.

Sotrovimab **must be diluted prior to administration** and must not be administered as an intravenous push or bolus.

Follow local SOPs/site processes to maintain the sotrovimab dose at **18-25°C during transport** to the clinic for administration.

- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab **up to 4 hours** at room temperature (20°C to 25°C [68°F to 77°F]), with the infusion starting within 2 hours of removal from refrigeration and completing (including flushing the line) within 4 hours of removal of the bag from refrigeration, or refrigerated **up to 24 hours** (2°C to 8°C [36°F to 46°F]).

Equipment required for IV administration of a 2000mg dose:

- Pre-filled 100mL 0.9% saline infusion bags **OR** empty 100mL infusion bags and bulk normal saline
- Bag spike
- Venting dispensing pin
- 10mL, 30mL, and 50mL sterile syringes
- 0.2µm in-line filter (not required but recommended)
- 21-gauge stainless steel sterile needles
- Sterile infusion set
- Individual protective equipment
- Polypropylene Syringe
- Infusion pump for dosing (flow rate of 50 - 200mL/hr)
- Amber UV light-inhibiting (UVLI) sleeve to protect the study drug infusion bag from light during infusion.

If available, it is recommended to use a laminar flow hood for dose solution preparations. Infusions must be prepared aseptically by the pharmacist/designated site staff. Aseptic technique must be strictly observed throughout the preparation process.

Preparation of Each Sotrovimab (VIR-7831) Dose (2000mg):

1. Complete the infusion bag label for VIR-7831 with the following information using a permanent black marker:
    a. Participant study ID number
    b. Site number where the infusion will be administered.

2. Remove four (4) vials of study drug from refrigeration. Allow the vials to equilibrate to ambient room temperature, protected from light, for at least 15 minutes.

3. Visually inspect the vials for 5 seconds to ensure it is free from particulate matter and that there is no visible damage to the vial.

4. Gently swirl the vial several times before use without creating air bubbles.

a. **Do not shake or vigorously agitate the vial**.
b. If a vial is identified to be unusable:

    a. Take a photo of the damaged vial, if possible.
    b. Record details of the vial for accountability purposes.
    c. Retrieve a new vial and restart the preparation.
    d. Destroy the damaged vial per institutional policies and procedures.
    e. Follow the pharmacy procedure for updating study drug inventory.

5. The intravenous (IV) solution can be prepared using either empty sterile 100mL infusion bags or pre-filled 100mL infusion bags (using aseptic precautions to prevent contamination).

<u>Use of a pre-filled, 100mL infusion bag</u>:

- Using an appropriately sized fresh syringe and 21-ga needle, draw 32mL of normal saline from the infusion bag.
- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from the each of the 4 vials of study drug.
- Inject 8mL of study drug from each of the 4 vials into the infusion bag via the septum to bring the total volume to approximately 100mL.
- Record the time the vials were punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UVLI sleeve).
- Discard any unused portion left inside the vials, as the product contains no preservative. The study drug inside each vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

<u>Use of an empty sterile 100mL infusion bag</u>:

- Use a 10mL syringe fitted with a 21-ga needle to draw 8mL from each of the 4 vials of study drug.
- Inject 8mL of study drug from each of the 4 vials into the empty infusion bag via the septum, for a total of 32 mL of study drug in the infusion bag.
- Using an appropriately sized fresh syringe and 21-ga needle, add 68mL of normal saline to the infusion bag via the septum to bring total volume to approximately 100mL.
- Record the time the vials were punctured on the infusion bag label using a permanent black marker (this information MUST be visible through the amber UVLI sleeve).

- Discard any unused portion left inside the vials, as the product contains no preservative. The study drug inside each vial is single use only and should only be used for one study participant.
- Prior to the infusion, gently rock the infusion bag back and forth by holding the prepared bag in two hands and gently move one hand down to get the fluid to move down and move the other hand up to get the fluid to move up. Repeat this action 3 to 5 times. DO NOT invert the infusion bag. Avoid forming air bubbles. Make sure to efficiently homogenize in areas of low solvent flow access around injection ports.
- An amber UV light-inhibiting (UVLI) sleeve should be used to protect the infusion bag containing diluted study drug from light during infusion.

8. Complete the infusion bag label for Sotrovimab (VIR-7831) with the following information using a permanent black marker. At a minimum the labels should contain the following information:

STUDY 14210 OPEN-LABEL MEDICATION
Sotrovimab (VIR-7831)
Subject ID #: .....

Study Site #: .....
Visit #: .....
Date: .....
Lot #: …….....

Time when vial was punctured for intravenous infusion: .....
Time IV bag preparation complete: .....
Expiration time: .....
Prepared by: .....

9. Apply the infusion bag label to the infusion bag.

10. Details of dose preparation should be recorded on the Dose Preparation Form in the Pharmacy Manual or site equivalent. For each dose preparation, a new copy of this form is used to record the date, the participant number, the dosing day/week, the the number of vials used, the time of dose preparation, the expiration time and the name and signature of the person preparing the dose.

11. Attach an infusion set to the infusion bag. Follow institutional policy for the use of an in-line filter for administration.

12. Follow institutional procedures for priming the infusion set and programing the infusion pump.

Sotrovimab must be diluted prior to administration and must not be administered as an intravenous push or bolus.

Follow local SOPs/site processes to maintain the sotrovimab dose at 18-25°C during transport to the clinic for administration.

- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]), with the infusion starting within 2 hours of removal from refrigeration and completing (including flushing the line) within 4 hours of removal of the bag from refrigeration, or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

8.1.8. Administration

500mg dose: Sotrovimab will be administered as an IV infusion over 30 minutes, followed by a one-hour monitoring period, as outlined in the Pharmacy Manual. Special IV tubing is not required; filtration with a 0.2 micron in-line filter is recommended but not required.

2000mg dose: The higher 2000mg dose of sotrovimab will be administered as an IV infusion over 60 minutes, followed by a 1-2-hour monitoring period, as outlined in the Pharmacy Manual. Special IV tubing is not required; filtration with a 0.2 micron in-line filter is recommended but not required.

8.1.9. Ordering

A drug supply request form will be sent to GSK/Vir to request vials of study drug (sotrovimab 500mg in 8mL (62.5 mg/mL)) by each site investigator, as needed. Study drug will be shipped at a temperature of 2°C to 8°C [36°F to 46°F] to investigators or designees at each site at regular intervals or as needed during the study.

8.1.10. Accountability

All drug accountability records must be kept up to date. Investigators, or a responsible party designated by the investigator, at each site must be able to account for all opened and unopened study drug, with accountability forms containing dates, quantity of study drug vials, and the name of the study medication as they are:

- Dispensed to each study subject
- Disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor-investigator, sponsor, or designees, including study monitors, and by regulatory agency inspectors as needed. It is recommended but not mandatory to save study drug vials for accountability purposes. Copies of the accountability records must be provided to the sponsor-investigator at the conclusion of the study. Sites may use site-specific accountability logs, as long as it is substantially equivalent to the accountability log provided in the pharmacy manual.

8.1.11. Destruction and Return

At specified time points during the study (e.g. at the site close-out visit, following drug reconciliation and documentation by the site monitor), all opened and unopened study drug will be destroyed at the site with approval of the sponsor or returned to the sponsor or designee.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Biomarker Studies

N/A

9.2. Laboratory Correlative Studies

N/A

9.3. Special Studies

N/A

10. STUDY CALENDAR

See pages 46-48 below.

Day	Screen	Treatment Day 1 (TD1)			Follow-Up Period 1[a]					Treatment Day 2 (TD2)			Follow-Up Period 2										EDC Timepoints
	(-)7 to 1	Pre-dose	Dose	Post-Dose	11	29	42	59	84	Pre-dose	Dose	Post-Dose	TD2 +3	TD2 +11	TD2 + 29	TD2 +42	TD2 +59	TD2 +84	TD2 +112	TD2 +140	TD2+168 / EOT	TD2 + 252/EOS	
Week		1			2	4	6	8	12	12			TD2 + 0	TD2 +2	TD2 +4	TD2 +6	TD2 +8	TD2 +12	TD2 +16	TD2 +20	TD+24	TD2 +36	
Visit Number[b]		1			2	3	4	5	6	7			8	9	10	11	12	13	14	15	16	17	
Window (Days)		±3			± 3	± 3	± 3	±3	±3	-4 (weeks)/ +2 (weeks)			-1/+2	±3	±3	±3	±3	±3	±3	±3	±3	±7	
Screening Only																							
Inclusion/Exclusion Criteria[c]	X																						Screening
SARS-CoV-2 Spike Antibody	X																						Screening
Informed Consent[d]	X																						Screening
Day 1 Only[e]																							
Demographics		X																					Baseline
Medical History[f]		X																					Baseline
Height and Weight		X																					Baseline
SARS-CoV-2 Vaccination History		X																					Baseline
Verification of Inclusion/Exclusion Criteria[g]		X																					Baseline
Treatment																							
Study Drug Administration			X								X												TD1, TD2
Safety and Tolerability Assessments																							
Vital Signs[h]		X		X	X	X				X		X	X[i]	X	X						X		TD1 (pre- and post-dose), V2, V3, TD2 (pre- and post-dose), V8, V9, V10, V16
Physical Exam		X								X											X		TD1, TD2, V16
Targeted Exam[j]					X	X							X[i]	X	X								V2, V3, V8, V9, V10
Karnofsky Performance Status		X								X											X		TD1, TD2, V16
12-Lead ECG		X								X											X		TD1, TD2, V16
Pregnancy Test[k]		X								X													TD1, TD2

Day	Screen	Treatment Day 1 (TD1)			Follow-Up Period 1[a]					Treatment Day 2 (TD2)			Follow-Up Period 2										EDC Timepoints
	(-)7 to 1	Pre-dose	Dose	Post-Dose	11	29	42	59	84	Pre-dose	Dose	Post-Dose	TD2 +3	TD2 +11	TD2 + 29	TD2 +42	TD2 +59	TD2 +84	TD2 +112	TD2 +140	TD2+168 / EOT	TD2 + 252/EOS	
Week		1			2	4	6	8	12	12			TD2 + 0	TD2 +2	TD2 +4	TD2 +6	TD2 +8	TD2 +12	TD2 +16	TD2 +20	TD+24	TD2 +36	
Visit Number[b]		1			2	3	4	5	6	7			8	9	10	11	12	13	14	15	16	17	
Window (Days)		±3			± 3	± 3	± 3	±3	±3	-4 (weeks)/ +2 (weeks)			-1/+2	±3	±3	±3	±3	±3	±3	±3	±3	±7	
Local Laboratory testing		X				X				X			X[i]		X						X		TD1, V3, TD2, V8, V10, V16
Targeted Concomitant Medications	←																					→	All visits
TEAE/AESI Monitoring	←																					→	All visits
SAE Monitoring	←																					→	All visits
Serum ADA		X				X				X					X						X		TD1, V3, TD2, V10, V16
Phone Call Follow-up Visit							X	X[l]	X[m]							X	X[n]	X	X	X		X	V4, V5, V6, V11, V12, V13, V14, V15, V17
Serum for PK Assessment				X	X	X		X[o]		X		X		X	X		X[p]				X		TD1, V2, V3, V5, TD2, V9, V10, V12, V16
Biweekly Anterior Nasal Swab SARS-CoV-2 RT-PCR[q]	←																					→	All visits
COVID-19 Symptom Assessment[r]	←																					→	All visits
SF-36 Quality of Life Assessment		X								X											X		TD1, TD2, V16

Day	Screen	Treatment Day 1 (TD1)			Follow-Up Period 1[a]					Treatment Day 2 (TD2)			Follow-Up Period 2										EDC Timepoints
	(-)7 to 1	Pre-dose	Dose	Post-Dose	11	29	42	59	84	Pre-dose	Dose	Post-Dose	TD2 +3	TD2 +11	TD2 + 29	TD2 +42	TD2 +59	TD2 +84	TD2 +112	TD2 +140	TD2+168 / EOT	TD2 + 252/EOS	
Week		1			2	4	6	8	12	12			TD2 + 0	TD2 +2	TD2 +4	TD2 +6	TD2 +8	TD2 +12	TD2 +16	TD2 +20	TD+24	TD2 +36	
Visit Number[b]		1			2	3	4	5	6	7			8	9	10	11	12	13	14	15	16	17	
Window (Days)		±3			± 3	± 3	± 3	±3	±3	-4 (weeks)/ +2 (weeks)			-1/+2	±3	±3	±3	±3	±3	±3	±3	±3	±7	
NIAID-OS Ordinal Scale[s]	←																					→	Only if subjects develop COVID-19
Transplant-Associated Endpoints[t]	←																					→	All visits

a: The duration of Follow-Up Period 1 was determined by theoretical modeling of the duration of efficacy of sotrovimab as antiviral prophylaxis in the setting of the rising prevalence of the Omicron BA.2 subvariant.
b: Visits in green are **in-person**, visits in red are **phone/remote** visits, and the day 59 visit in yellow is in-person for the 10 patients in the lead-in PK cohort and phone/remote for all other study subjects. The yellow visits at Visits 8 and 12 are in-person for the first 10 participants to receive the second dose of sotrovimab at the 2000mg dose and not required for other study participants. Participants will complete the Day 84 visit if they have not received their second dose before 12 weeks.
c: Inclusion and exclusion criteria are listed in **Section 3.1** and **3.2**.
d: The first 10 patients enrolled in the study will provide additional consent for an extra in-person visit on day 59 for a blood draw for serum PK testing to determine the optimal dosing interval between doses 1 and 2 of sotrovimab. The first 10 participants to receive their second dose of sotrovimab will consent for the 2-hour post-dose observation period and 2 additional in person-visits (visit 8 and 12).
e: Screening and baseline procedures may be completed on the same day.
f: Refer to **Section 11.1.2** for details of medical history recording.
g: Inclusion/exclusion should be confirmed again on Treatment Day 1 if Screening is not performed at the same visit as Treatment Day 1. SARS-CoV-2/COVID-19 symptom assessment should be re-evaluated using the Clinical Signs and Symptoms Assessment in **Appendix D**.
h: Vital sign collection is described in **Section 11.1.6**.
i: Only necessary for the first 10 participants to receive their second sotrovimab dose.
j: A description of targeted exam parameters can be found in **Section 11.1.7**.
k: Pregnancy testing will be performed only in women of childbearing potential. A negative test is needed to administer study drug.
l: Not needed if patient consented to lead-in PK cohort.
m: Only necessary for patients who receive their second dose of sotrovimab after day 84.
n: Not needed if patient is one of the first 10 patients to receive their second sotrovimab dose.
o: Only necessary for the 10 study subjects enrolled in the lead-in PK cohort.
p: Only necessary for the first 10 participants to receive their second sotrovimab dose.
q: Self-administered swabs will always be completed at home even if it is a week the patient is seen at the study site.
r: COVID-19 symptoms should be assessed using the Clinical Signs and Symptoms Assessment in **Appendix D**.
s: To be completed only in study subjects diagnosed with COVID-19 during the follow up period, at the end of hospitalization, or for those who do not require hospitalization, 14 days after diagnosis. NIAID-OS can be found in **Appendix E**. If feasible, patients who develop COVID-19 will be asked to come in for an end of treatment visit, including a PK assessment, as close to the time when they are diagnosed with COVID-19 as possible.
t: Description of transplant-associated endpoints can be found in **Section 11.1.15**.

11. MEASUREMENT OF EFFECT

11.1. Safety and Tolerability Assessments

Study visits are outlined in **Section 10** (the Study Calendar). Study subjects should follow the study schedule as outlined as closely as possible. Unscheduled visits may be performed in order to review and/or repeat abnormal safety laboratory results, to perform SARS-CoV-2 testing if patients report symptoms potentially suggestive of COVID-19 infection, to follow up SAEs or AEs, or for other reasons deemed necessary by the principal investigator.

The following parameters will be assessed to establish the baseline health status of study participants and examine study participant safety over the study period.

Treatment Day 1-Specific Procedures

11.1.1. Demographics

Standard demographic parameters (e.g., age, sex, race, ethnicity) will be recorded in the eCRF.

11.1.2. Medical History

Relevant medical conditions that existed or were diagnosed prior to the signing of the informed consent form will be recorded as part of the study subject's medical history in the eCRF. Abnormal laboratory values and vital signs observed at the time of informed consent will also be recorded as medical history. Any subsequent worsening (clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug will instead be recorded as TEAEs, if they fulfill criteria.

A targeted past medical history will be recorded in the eCRF, including:

- Immunocompromising conditions
- History of prior COVID-19 infection
- COVID-19 risk factors, based on the Centers for Disease Control and Prevention (CDC) list of patients at risk of severe COVID-19 illness [14]:
    - Malignancy
    - Solid organ or hematopoietic cell transplant
    - Chronic kidney disease
    - Chronic lung disease (including moderate to severe asthma, bronchiectasis, bronchopulmonary dysplasia, chronic obstructive pulmonary disease (including emphysema and chronic bronchitis), cystic fibrosis, pulmonary embolism, and pulmonary hypertension)
    - Heart conditions (including congestive heart failure, coronary artery disease, cardiomyopathies, hypertension)
    - Diabetes (type 1 or 2)

  - Elevated BMI - overweight (25 kg/m^2 < BMI < 30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2)
  - Cerebrovascular disease or stroke
  - Chronic liver disease or cirrhosis (including alcohol-related liver disease, non-alcoholic fatty liver disease, or autoimmune hepatitis)
  - HIV infection
  - Mental health conditions (including depression, schizophrenia spectrum disorders)
  - Sickle cell disease or thalassemia
  - Down syndrome
  - Current or former cigarette smoking
  - Substance use disorders
  - Tuberculosis
- Menopausal history

11.1.3. Weight and Height

Weight and height will be recorded on Treatment Day 1 prior to the first dose of sotrovimab, with BMI calculated from these parameters.

11.1.4. SARS-CoV-2 Vaccination History

SARS-CoV-2 vaccines previously received by each study subject will be recorded, including the type of vaccine and dates received. Any SARS-CoV-2 vaccines received during the study period will be recorded as concomitant medications.

11.1.5. Verification of Inclusion and Exclusion Criteria

If Screening and Treatment Day 1 procedures are not performed on the same day, inclusion and exclusion criteria (outlined in **Section 3.1** and **3.2**) will need to be verified on Treatment Day 1 prior to sotrovimab dosing.

Safety and Tolerability Parameters

11.1.6. Vital Signs

Vital signs will be collected according to the schedule outlined in the Study Calendar (**Section 10**), with collection points prior to and following sotrovimab dosing on Treatment Day 1 and the second sotrovimab dosing day, and on day 11 and 29 after the first dose of sotrovimab, day 11 and 29 after the second dose of sotrovimab, and at the EOT visit. The 10 patients in the 2000mg dose lead-in safety cohort will also have vital signs measured on their Treatment Day 2 + 3 day visit.

Vital signs will include body temperature, heart rate, blood pressure, oxygen saturation (SpO_2), and respiratory rate. Vital signs should be obtained after 5 minutes of rest (supine or sitting). Vitals signs that are obtained following each sotrovimab dose should be obtained **within 30 minutes** after drug administration has been completed.

The method used to obtain body temperature should be consistent across all visits for a patient.

Resting SpO_2 (%) will be measured using a fingertip oximeter or similar device. In the event that a patient requires supplemental oxygen, oxygen flow rate will be measured (L/min). If a patient is mechanically ventilated, FiO2 will be measured. The oxygen device used should be recorded.

11.1.7. Physical Exam

A **comprehensive physical exam** will be performed prior to the first and second dose of sotrovimab and on day 168 after the second sotrovimab dose (the EOT visit), and a **targeted physical exam** will be performed on day 11 and 29 after the first dose of sotrovimab, and day 11 and 29 after the second dose of sotrovimab. The 10 patients in the 2000mg dose lead-in safety cohort will also have a targeted physical exam on their Treatment Day 2 + 3 day visit.

The **targeted physical examination** will include, but is not limited to assessment of the following:

- Vital signs
- General appearance of the study subject
- Lung exam (e.g. crackles, rhonchi, diminished breath sounds)
- Skin exam (e.g. urticaria, ulcerations, erythema multiforme, maculopapular rashes).

11.1.8. Karnofsky Performance Status

Each study subject's Karnofsky performance status (**Appendix A**) will be assessed prior to the first and second dose of sotrovimab and on day 168 after the second sotrovimab dose (the EOT visit).

11.1.9. Electrocardiogram

A single 12-lead ECG will be obtained and assessed for clinical abnormalities prior to the first and second dose of sotrovimab, and on day 168 after the second sotrovimab dose (the EOT visit), recording heart rate, PR interval, QRS duration, and QTc in the eCRF. We will use the Fridericia formula to determine the QTcF.

11.1.10. Pregnancy Testing and Pregnancy Reporting

Pregnancy testing is required in women of childbearing potential. A negative urine or serum hCG test is required in all women of childbearing potential prior to each dose of sotrovimab, on Treatment Day 1 and Treatment Day 2.

Study participants who are women of childbearing potential should use two highly effective methods of contraception, as described in **Section 3.1.3**, throughout the study period up to 36 weeks after the last dose of sotrovimab (the end of study remote visit).

Study staff should be informed immediately if a woman of childbearing potential becomes pregnant or starts breastfeeding during the study period.

11.1.11. Local Laboratory Testing

All laboratory testing will be completed locally at each site. Clinical laboratory parameters will be measured at the baseline/Treatment Day visit prior to the administration of the first sotrovimab dose, day 29, at the Treatment Day 2 visit prior to the administration of the second sotrovimab dose, day 29 after the second sotrovimab dose, and day 168 after the second sotrovimab dose (the EOT visit). The 10 patients in the 2000mg dose lead-in safety cohort will also have an additional set of local laboratory values measured on their Treatment Day 2 + 3 day visit.

Laboratory parameters that will be obtained at each of these time points include:

- Hematology:
    - Complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit, platelet count)
    - Differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Blood Chemistry:
    - Basic metabolic panel (sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), creatinine, glucose)
    - Liver function tests (alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, total protein, albumin, globulin).

11.1.12. Targeted Concomitant Medications

Any treatment administered from the first dose of sotrovimab on Treatment Day 1 to the end of the study period will be considered a concomitant medication. This includes medications that study subjects were taking from 30 days prior to consenting to participate in the study and are ongoing during the study.

A targeted list of the following concomitant medications will be recorded in the eCRF at each in-person and remote study visit:

- Putative COVID-19 treatments (e.g. remdesivir, convalescent serum, intravenous immunoglobulin (IVIG), IL-6 receptor inhibitors (e.g. sarilumab, tocilizumab), JAK inhibitors (e.g. baricitinib), ivermectin), 28 days prior to enrollment and during the study period.
- SARS-CoV-2 vaccination doses.
- Antipyretics (e.g. aspirin, acetaminophen, ibuprofen).
- Anticoagulants (e.g. enoxaparin, warfarin, rivaroxaban).
- Immunosuppressants (e.g. cyclosporine, corticosteroids, methotrexate, mycophenolate mofetil, tacrolimus, sirolimus, Bruton tyrosine kinase inhibitors, ruxolitinib, venetoclax).
- Interferon beta.
- Theophylline.
- Antiepileptics (e.g. carbamazepine, divalproex, phenytoin).

- Antiarrhythmics (e.g. digoxin, disopyramide, procainamide, amiodarone).
- Antiviral, antibacterial, and antifungal drugs.
- Antiparasitics (e.g. chloroquine or hydroxychloroquine).
- Angiotensin receptor blockers (e.g. losartan, valsartan).
- Angiotensin converting enzyme inhibitors (e.g. benazepril, lisinopril)
- Biological therapies (eg. rituximab and other anti-CD20 antibodies, alemtuzumab, interferon-gamma inhibitors).

11.1.13. Adverse Event Monitoring

Grade 3-4 treatment-emergent adverse events (TEAEs), as defined using DAIDS grading criteria [66], and treatment-emergent serious adverse events (SAEs), as defined using DAIDS grading criteria and **Section 7**, will be collected from patient consent until the end of study remote visit (36 weeks after Treatment Day 2). Patients will be solicited for the development of any AEs at each in-person or remote visit, and any unsolicited AEs reported will be investigated further.

11.1.14. Adverse Events of Special Interest (AESI) Monitoring

Adverse events of special interest (AESI) will be collected from patient consent until the end of study visit (36 weeks after Treatment Day 2).

Adverse events of special interest are defined as relevant known toxicities of other therapeutic monoclonal antibodies that will be monitored by the study team during the study.

As outlined in **Section 7.1.1**, adverse events of special interest for sotrovimab include:

- Hypersensitivity reactions or anaphylaxis. See **Section 5.3** for guidance on the management of suspected hypersensitivity reactions or anaphylaxis.
- Infusion related reactions. See **Section 5.3** for guidance on the management of suspected infusion-related reactions.
- Immunogenicity-related adverse events (development of ADA). See **Section 7.1.1** for more details.

Adverse events potentially related to antibody-dependent enhancement of COVID-19 infection. See **Section 7.1.1** for more details.

11.1.15. Transplant-Associated Endpoints

Study participants who are solid organ transplant (SOT) or hematopoietic cell transplant (HCT) recipients will be assessed at each follow-up visit for:

(1) New-onset cellular or antibody-mediated rejection events in solid organ transplant (SOT) recipients, with evidence of acute or chronic rejection on allograft biopsy samples or evidence of donor-specific antibodies (DSA) in serum samples obtained for workup of suspected antibody-mediated rejection.

(2) New-onset or worsening graft-versus-host disease in hematopoietic cell transplant (HCT) recipients.
(3) New-onset allograft or stem cell failure with the need for re-transplantation in HCT recipients.

11.2. Drug Concentration Measurements for Pharmacokinetic Assessment

Serum sotrovimab levels will be measured for pharmacokinetic (PK) assessment within 1 hour after the first sotrovimab infusion on Treatment Day 1, 11, 29, 59 (only the 10 patients in the initial lead-in cohort will have a serum sotrovimab pharmacokinetic assessment on day 59), prior to the second dose of sotrovimab on Treatment Day 2, within 1 hour after the second sotrovimab infusion, and 11, 29, 59 (only the 10 patients in the 2000mg dose lead-in cohort will have a serum sotrovimab pharmacokinetic assessment on Treatment Day 2 + 59 days), and 168 days after the second sotrovimab dose.

The actual date and time of each sample will be recorded in the eCRF.

The PK parameters to be determined for sotrovimab may include, but are not limited to: maximum sotrovimab serum concentration (C_{max}), time to maximal sotrovimab serum concentration (t_{max}), C_{max} vs. dose, minimal sotrovimab serum concentration (C_{min}), last serum sotrovimab concentration (C_{last}), time of last measurable sotrovimab concentration (t_{last}), area under the curve extrapolated to infinity ($AUC_{(0-\infty)}$), $AUC_{(0-\infty)}$ vs. dose, half-life ($t_{1/2}$), and concentration in serum 28 days after dosing (C_{28}). Selected PK parameters will be summarized by descriptive statistics for the selected cohort. All parameters will be summarized (mean, standard deviation (SD), % coefficient of variation (CV), range, median, and number of samples).

11.3. COVID-19 and Quality of Life Assessments

11.3.1. Self-Collected Anterior Nasal Swabs for SARS-CoV-2 RT-PCR

Patients will collect self-administered anterior nasal swabs bi-weekly over the study period through the EOT visit 168 days after Treatment Day 2 using the binx health At-Home Nasal Swab COVID-19 Sample Collection Kit, which has Emergency Use Authorization (EUA) for the self-collection of anterior nasal swab specimens at home [78-79]. A prepaid shipping envelope will be provided with each swab, and patients will submit these swabs to UPS. These dry swab specimens can be transported at ambient temperature for testing at an authorized, CLIA-certified laboratory, with molecular diagnostic testing performed using an *in vitro* diagnostic (IVD) assay that has received FDA EUA for the diagnosis of SARS-CoV-2. In patients who develop SARS-CoV-2 infection during the follow-up period, with positive binx health At-Home Nasal Swabs assays, the specimen will be retained so spike genes can be sequenced to assess for mutations that might confer resistance to sotrovimab or other antibody therapies.

11.3.2. COVID-19 Symptom Assessment

An assessment of COVID-19-related symptoms will be performed at each in-person or remote study visit, using the CDC's list of symptoms commonly associated with COVID-19 [8]:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea.

Study participants will be asked if they have any of these symptoms *de novo* or worsening from their baseline at each in-person and remote visit, using a questionnaire (**Appendix D**). Due to the contagiousness of the BA.2 Omicron variant, the study team will also proactively reach out to study participants on a weekly basis by telephone or email to assess for the presence of COVID-19 symptoms following the second sotrovimab dose. If they report any of these symptoms (new or worsening from baseline) at an in-person visit, they will have a nasopharyngeal swab obtained for local laboratory RT-PCR testing for SARS-CoV-2. If they report any of these symptoms at a remote visit, they will be asked to go to a local laboratory for SARS-CoV-2 RT-PCR testing.

Study participants will also be asked to report any emergency department (ED) visits and inpatient hospitalizations, including intensive care hospitalizations, over the study period.

The greatest extent of COVID-19 symptoms, as assessed using the 8-point National Institute of Allergy and Infectious Diseases ordinal scale (NIAID-OS), will be assessed in each study subject who develops COVID-19, either at the end of hospitalization or, in those who are not hospitalized, 14 days after the diagnosis of COVID-19 (**Appendix E**) [80].

In addition to symptom-triggered testing, study participants will obtain self-collected anterior nasal swabs every other week for SARS-CoV-2 RT-PCR testing, using the binx health At-home Nasal Swab COVID-19 Sample Collection Kit and user interface, available under a FDA EUA [78]. These samples will be shipped at ambient temperature to authorized laboratories designated by binx health, Inc., which are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and meet requirements to perform high complexity tests and run the specimens collected using the binx health sample collection kit, using an *in vitro* diagnostic (IVD) molecular

test (RT-PCR) for SARS-CoV-2 [79]. Study participants and the study team will receive results of this biweekly molecular testing.

Study subjects with any positive RT-PCR SARS-CoV-2 testing result over the study period will be considered to have COVID-19, with subjects reporting any new or worsening symptoms associated with COVID-19 temporally related to their positive result considered to have symptomatic COVID-19 and patients without any new or worsening symptoms temporally related to their positive result considered to have asymptomatic COVID-19 infection [8].

11.3.3. NIAID-OS Ordinal Scale in Study Subjects Who Develop COVID-19

In patients who are diagnosed with COVID-19 during the follow-up period, greatest extent of COVID-19 symptoms, as assessed using the 8-point National Institute of Allergy and Infectious Diseases ordinal scale (NIAID-OS), will be determined at the end of hospitalization or, in those who do not require hospitalization, 14 days after the diagnosis of COVID-19 (**Appendix E**) [80].

11.3.4. Quality of Life Questionnaire

Health-related quality of life measures will be assessed prior to the first and second dose of sotrovimab and on day 168 after the second sotrovimab dose (the EOT visit) using the RAND 36-Item Short Form Health Survey (SF-36) instrument [81]. Surveys will be completed at study visits by the patient and stored in patient binders, with answers entered into the eCRF.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7** (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1. Method

Syneos Health will provide electronic data capture services. Syneos Health will monitor and perform quality checks on data collected for this study.

12.1.2. Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms into the electronic case report forms designed to capture specific and relevant study data.

Case Report Form Requirements

Data obtained during the study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for every patient enrolled in the study **within 72 hours** of each study visit or phone call. The investigator must

ensure the accuracy, timeliness, and completeness of the data reported to the sponsor-investigator in the eCRFs. After reviewing the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record.

Any corrections to the eCRF will be entered by the investigator or an authorized designee. Any changes, including the date and person performing these corrections, will be visible via the audit trail integrated in the EDC system. For corrections made via data queries, the reason for any alterations must be provided.

Investigators are required to prepare and maintain adequate and accurate patient records, or source documents. Each site is responsible for ensuring quality within their records and systems and is accountable for ensuring that all source data and eCRF data are entered in an accurate, timely, and complete manner. Investigators at each site must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor-investigator and regulatory authorities.

12.2. Data Safety Monitoring

This is a single-arm, open-label, non-randomized study conducted at three sites within DF/HCC (Dana-Farber/Harvard Cancer Center), with the sponsor-investigator and central study team having access to all data, so a Data and Safety Monitoring Committee has been deemed to be unnecessary. Instead, a qualified independent study monitor (ISM) will evaluate enrollment data and all grade 2 or higher unexpected adverse events in the study twice a year. The ISM will issue a written monitoring report to the study team after each review, addressing any questions about participant safety with the sponsor-investigator and study team and issuing a final recommendation as to the study's continuation.

Monitoring of Study Sites

In accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6, the sponsor-investigator is responsible for quality control and quality assurance to ensure that the study is conducted and the data are generated, recorded, and reported in compliance with the protocol, good clinical practice (GCP), and any applicable regulatory requirements.

Study monitors will conduct remote and in-person monitoring visits to each site periodically during the study. This study will use the principles of risk-based monitoring (ICH), with the monitoring strategy for any given site varying based on site risk indicators. Investigators at each site must allow study-related monitoring and:

- Provide access to all necessary facilities, study data, and documents for internal or external inspection or audit as needed.
- Communicate any information arising from these inspections to the sponsor-investigator immediately.

- Take all appropriate measures requested by the sponsor-investigator and/or designees or auditor to resolve any problems found during the audit or inspection.

Study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the currently approved version of the protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Documents subject to audit or inspection include (but are not limited to) all source documents, eCRFs, medical records, correspondence, informed consent forms (ICFs), IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage may also be subject to inspection. In addition, representatives of the sponsor-investigator may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution. In all instances, the confidentiality of the data must be respected.

12.3. Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

While the current medical approach to preventing COVID-19 consists of several widely available vaccine products, individuals with impaired humoral immunity due to a range of immunocompromising conditions may fail to develop detectable antibodies even in the setting of repeat vaccination. As such, alternative approaches to prevent SARS-CoV-2 infection are needed for this population. Sotrovimab is an investigational monoclonal antibody that targets a highly conserved epitope on the spike glycoprotein of SARS-CoV-2 and has received FDA EUA for the treatment of mild-to-moderate COVID-19 [49]. This is a Phase II open-label safety and tolerability study of sotrovimab for the pre-exposure prophylaxis of SARS-CoV-2 infection in immunocompromised individuals.

13.1. Study Design/Endpoints

The **primary objective** of this study is to evaluate the safety and tolerability of sotrovimab as pre-exposure prophylaxis for immunocompromised individuals. As such, the primary endpoints of this study are:

(1) The safety and tolerability of sotrovimab in immunocompromised patients with impaired humoral immunity against SARS-CoV-2 as defined by:
    a. The proportion of study subjects with treatment-emergent grade 3-4 adverse events (TEAEs), as defined in the DAIDS grading criteria [66].

b. The proportion of study subjects with treatment-emergent serious adverse events (SAE), as defined in **Section 7**.
c. The proportion of study subjects with adverse events of special interest (AESI), including infusion-related and hypersensitivity reactions, the development of anti-drug antibody (ADA) levels, and antibody-dependent enhancement (ADE) of COVID-19 disease, as outlined in **Section 7.1.1**.

(2) Evaluation of the pharmacokinetics of sotrovimab in immunocompromised patients with impaired humoral immunity against SARS-CoV-2.

The **secondary objectives** of this study are to describe COVID-19 infection and quality-of-life outcomes in immunocompromised individuals receiving sotrovimab prophylaxis. The secondary endpoints of this study relevant to COVID-19 infection include:

(1) The proportion of study subjects that develop COVID-19 (of any severity) over the study follow-up period.
(2) The proportion of study subjects with severe COVID-19, with any of the following criteria:
    a. Dyspnea, respiratory rate of 30 or more breaths per minute, blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) < 300 mm Hg, or infiltrates in more than 50% of the lung field).
    b. Emergency department (ED) visit, inpatient hospitalization, or ICU hospitalization within 28 days of a new diagnosis of SARS-CoV-2.
    c. Need for new or increasing supplemental oxygen, OR mechanical ventilation within 28 days of a new diagnosis of SARS-CoV-2.
    d. Death due to any cause during the study follow-up period.
(3) In patients who develop COVID-19, the greatest extent of COVID-19 symptoms, as assessed using the 8-point National Institute of Allergy and Infectious Diseases ordinal scale (NIAID-OS), assessed at the end of hospitalization or 14 days after the diagnosis of COVID-19 [80].
(4) Health-related quality of life measures using the Short Form Health Survey (SF-36) instrument, assessed at baseline, 12 weeks, and 24 weeks [81].

Exploratory objectives of this study are to describe transplant-specific outcomes in immunocompromised individuals receiving sotrovimab prophylaxis, including:

(4) The proportion of solid organ transplant (SOT) recipient study subjects with new-onset cellular or antibody-mediated rejection events.
(5) The proportion of hematopoietic cell transplant (HCT) recipients with new-onset or worsening graft-versus-host disease (GVHD).
(6) The proportion of HCT recipients with allograft or stem cell failure with the need for re-transplantation.

The study has a planned sample size of 93 participants and will accrue all participants within the first year of the study.

These participants will be accrued in three stages:

(1) A 10-patient pharmacokinetic lead-in cohort to determine the optimal dosing interval between two sequential doses of intravenous sotrovimab, administered as prophylaxis in immunocompromised patients with impaired humoral immunity to COVID-19.
(2) A 50-patient safety and tolerability lead-in cohort (including the 10 patients in the pharmacokinetic lead-in cohort) to examine the safety and tolerability of intravenous sotrovimab administered over a 30-minute infusion period.
(3) An expansion cohort for further assessment of the safety and tolerability of intravenous sotrovimab. If there are no grade ≥ 2 infusion-related reactions in the 50-patient safety and tolerability lead-in cohort, patients in this expansion cohort will receive their intravenous sotrovimab doses over a 15-minute infusion period; if there is at least one patient with a grade ≥ 2 infusion-related reaction, study subjects in the expansion cohort will continue to receive intravenous sotrovimab over a 30-minute infusion period.

The 10 patients in the 2000mg sotrovimab repeat dose lead-in cohort will inform the observation period for all patients who receive their 2000mg dose after these patients, with a 2-hour observation period following completion of the dose for these 10 patients, reduced to a one-hour period for all subsequent patients if there are no grade 3 or 4 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in this 2000mg dose lead-in safety cohort.

13.2. Sample Size, Accrual Rate and Study Duration

The planned sample size for this study will be 93 participants, all of whom will be accrued within 9-12 months, with follow-up visits for an additional 36 weeks after the last study subject receives their last sotrovimab dose, for a total study duration of approximately 2 years. A total cohort size of 93 subjects (inclusive of the 10 patients in the initial lead-in PK cohort and in the 2000mg dose lead-in cohort) will provide a suitably precise assessment of the descriptive safety and tolerability profile for a two-dose regimen of IV sotrovimab. This enrollment plan is consistent with similar ongoing clinical studies of COVID-19 prophylaxis and justified by the relatively broad inclusion criteria for the study, encompassing multiple distinct subgroups of immunocompromised patients. The following table contains estimates of the precision in the estimated grade 3-4 TEAE rate.

Table 4. Precision in the Estimated Grade 3-4 Treatment-Emergent Adverse Event Rate with a Total Cohort Size of 93 Patients

AE Rate	Exact 95% Confidence Interval	Probability of Seeing at Least One Event

1%	(0.0%, 5.8%)	0.607
2%	(0.2%, 7.6%)	0.847
3%	(0.7%, 9.1%)	0.941
4%	(1.2%, 10.6%)	0.978
5%	(1.8%, 12.1%)	0.992

Patients who discontinue their participation in the study prematurely will not be replaced.

The study will end on the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up. The accrual targets by study subject race and ethnicity are as outlined in the table below:

Table 5. Study Accrual Targets by Race/Ethnicity

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	3	=	6
Not Hispanic or Latino	43	+	44	=	87
Ethnic Category: Total of all subjects	46	+	47	=	93
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	2	=	4
Black or African American	4	+	4	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	40	+	41	=	81
Racial Category: Total of all subjects	46	+	47	=	93
	(A1 = A2)		(B1 = B2)		(C1 = C2)

13.3. Stratification Factors

Where possible, all analyses will be conducted in the full cohort and separately, stratified by subtype of underlying immunocompromised status as follows: (1) solid organ transplant recipients, (2) participants with a history of hematologic malignancy requiring hematopoietic cell transplant and/or history of chimeric antigen receptor (CAR)-T cell therapy, and (3) participants with any other hematologic malignancy, autoimmune or inflammatory condition requiring either use of anti-CD20 monoclonal antibody or other immunosuppressive medication specifically associated with a blunted humoral immune response to SARS-CoV-2, as outlined in the inclusion criteria. These analyses, including comparisons of the primary and secondary outcomes of interest across these three groups, will permit an exploration of specific differences that may be present between subgroups with varying immunological deficits.

13.4. Interim Monitoring Plan

As detailed above, this study will unfold in stages. First, an analysis of the 10-patient pharmacokinetic lead-in cohort and theoretical pharmacokinetic modeling of the duration of the antiviral efficacy of sotrovimab based on the rising prevalence of the BA.2 variant will define the optimal dosing interval between two sequential doses of intravenous sotrovimab. The remaining participants will follow the dosing interval defined by this lead-in cohort. Second, the 50-patient safety and tolerability lead-in cohort (inclusive of these 10 patients) will inform the infusion period for the remaining participants. If there are no grade ≥ 2 infusion-related reactions in this initial group, patients in the expansion cohort will receive their intravenous sotrovimab doses over a 15-minute infusion period; however, if there is at least one patient with a grade ≥ 2 infusion-related reaction, study subjects in the expansion cohort will continue to receive intravenous sotrovimab over a 30-minute infusion period. These data will be reviewed by the study team. Finally, the 10 patients in the 2000mg sotrovimab dose lead-in cohort will inform the observation period for all patients who receive their 2000mg dose after these patients, with a 2 hour observation period following completion of the 2000mg dose for these 10 patients, reduced to a one-hour period for all subsequent patients if there are no grade 3 or 4 infusion-related reactions or other SAEs potentially related to the sotrovimab dose in this 2000mg dose lead-in safety cohort.

13.5. Analysis of Primary Endpoints

No formal hypothesis tests will be performed and no formal significance tests for comparisons will be made. The primary safety and tolerability outcomes of interest will be displayed in the form of listings, frequencies, summary statistics, and graphs, where appropriate. Binary data will be presented in the form of counts and proportions and continuous data will be presented using descriptive statistics (N, mean, SD, median and range). Similarly, descriptive statistics will be provided for selected PK parameters of interest for the cohort. All PK parameters will be summarized in terms of means, standard deviation (SD), % coefficient of variation (CV), range, median, and number of samples. Interpretation of these safety and tolerability data and PK values will be informed by clinical expertise.

13.6. Analysis of Secondary Endpoints

The secondary endpoints of interest in this study will include: (1) COVID-19 infections over the study period and (2) self-reported quality of life measures over the course of the study. COVID-19 infections in this cohort will be summarized using standard descriptive statistics including counts and proportions where applicable. Logistic regression models will be used to examine sociodemographic and health-related factors associated with incident COVID-19 infection in this population over the study period. Covariates such as age, sex, type of immunocompromising condition, prior vaccination status and body mass index will be assessed in these models. Changes in self-reported quality of life from baseline to the study mid-point and baseline to endline, as assessed by the SF-36 instrument, will be analyzed descriptively, and where appropriate, graphically visualized from baseline to endline. A linear mixed model with a random slope for each participant and an unstructured correlation matrix will be used to examine changes in SF-36 continuous scores over time and include baseline demographic and relevant clinical parameters as fixed effects.

13.7. Reporting and Exclusions

13.7.1. Evaluation of Toxicity

All participants will be evaluable for the primary safety and tolerability endpoints from the time of their first treatment.

13.7.2. Evaluation of the Primary Efficacy Endpoint

This study does not include a primary efficacy endpoint.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A KARNOFSKY PERFORMANCE STATUS SCALE

Percent	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires considerable assistance, but is able to care for most of his/her needs
50	Requires considerable assistance, and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization indicated. Death not imminent
10	Moribund, fatal processes progressing rapidly
0	Dead

APPENDIX B MULTI-CENTER GUIDELINES

N/A

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

No formal interaction studies have been conducted with sotrovimab. Sotrovimab is neither renally excreted nor metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

APPENDIX D COVID-19 CLINICAL SIGNS AND SYMPTOMS ASSESSMENT

Patient Study ID: _____

Patient Initials: _____

Study Visit Number:_____

Date: _____

Investigator Signature: _____

Have you had any of the following symptoms in the past 14 days that are either **new** or **worsening**?

- ☐ Fever or chills
- ☐ Cough
- ☐ Shortness of breath or difficulty breathing
- ☐ Fatigue
- ☐ Muscle or body aches
- ☐ Headache
- ☐ New loss of taste or smell
- ☐ Sore throat
- ☐ Congestion or runny nose
- ☐ Nausea or vomiting
- ☐ Diarrhea
- ☐ **No new or worsening symptoms to report**

If you reported any new or worsening symptoms, could they be explained by any of your underlying medical conditions, current treatments, or relevant medical history? If yes, explain.

Investigator Judgement

- ☐ Screen pass
- ☐ Screen fail

APPENDIX E 8-POINT NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES ORDINAL SCALE (NIAID-OS) FOR THE ASSESSMENT OF CLINICAL STATUS IN PATIENTS WITH SARS-COV-2 INFECTION
[80]

NIAID-OS Scale Value	Scale Value Description
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities or/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8	Death