TITLE PAGE

Division: Pharma Research and Development
Information Type: Epidemiology PASS Protocol

Title:	Prospective cohort study to monitor the emergence of SARS-CoV-2 spike viral variants in immunocompromised non-hospitalised patients exposed to sotrovimab in Great Britain: LUNAR study

Compound Number:	GSK4182136
Development Phase	IV
Effective Date:	24 January 2023
Subject:	SARS-CoV-2 infection
Author(s):	PPD

Indication Studied: Early treatment for SARS-CoV-2 infection

PASS information *

Title	Prospective cohort study to monitor the emergence of SARS-CoV-2 spike viral variants in immunocompromised non-hospitalised patients exposed to sotrovimab in Great Britain: LUNAR study
Protocol version identifier	Version 2
Date of last version of protocol	04 May 2022
EU PAS (ENCEPP) register number	EUPAS46386
Active substance	Sotrovimab [recommended INN] (also known as VIR-7831 and GSK4182136) ATC code: J06BD05
Medicinal product	Xevudy™ 500 mg concentrate for solution for infusion
Product reference	PLGB 19494/0301
Procedure number	N/A
Marketing authorisation holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
Joint Post Authorisation Safety Study **PASS**	No

Research question and objectives	Amongst immunocompromised non-hospitalised patients treated with sotrovimab as part of standard clinical care: Primary Objectives: 1- Evaluate the proportion of patients eligible for sequence analysis that have any amino acid (AA) change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days) 2- Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) Secondary Objectives: 1. Evaluate the proportion of patients eligible for sequence analysis with variants of concern (VOC) and under investigation (VUI) on the earliest possible sample including baseline 2. Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by reverse transcriptase polymerase chain reaction (RT-PCR) 3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, intensive care unit [ICU] admission and death) through Day 28 post sotrovimab administration 4. Describe AA (detected at >5% allelic frequency) changes in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay 5. Describe AA changes in the consensus sequence (>50%) of SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads below the threshold for detection of AA changes at >5% allelic frequency but with sufficient levels to generate consensus sequencing data

Country of study	Great Britain
Author	PPD , PhD, PharmD, MPH PPD , Value Evidence and Outcomes

MARKETING AUTHORISATION HOLDER(S) *

Marketing authorisation holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
MAH contact person	PPD

TABLE OF CONTENTS

PAGE

1. LIST OF ABBREVIATIONS

AA	Amino Acid
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GB	Great Britain
GISAID	Global Initiative on Sharing All Influenza Data
GSK	GlaxoSmithKline
HCP	HealthCare Professional
HSA	Health Security Agency
HSI	Human Safety Information
IC	Immunocompromised
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PASS	Post Authorisation Safety Study
PCR	Polymerase Chain Reaction
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE(s)	Severe Adverse Event(s)
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMP	Safety Management Plan
SOP	Standard Operating Procedure
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
VOC	Variant of Concern
VUI	Variant Under Investigation
WHO	World health Organization

Trademark Information

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None

2. RESPONSIBLE PARTIES

Co-Principal Investigator: Professor Judith Breuer, University College London

Co-Principal Investigator: Dr David Mark Lowe, University College London

Qualified Person for Pharmacovigilance (QPPV): Heather Stein

SPONSOR SIGNATORY:

Title:	Prospective cohort study to monitor the emergence of SARS-CoV-2 spike viral variants in immunocompromised non-hospitalised patients exposed to sotrovimab in Great Britain: LUNAR study

Compound Number: GSK4182136

PPD

Myriam Drysdale
Scientific Lead, Epidemiology, VEO, GSK

Date

PPD

Melissa Van Dyke
Immunology Head, Epidemiology, VEO, GSK

Date

Heather Stein
TA Head, Global Safety, GSK

Date

SPONSOR INFORMATION PAGE

Study ID: 218407

Sponsor Legal Registered Address and Sponsor Contact Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Medical Monitor Contact Information: Medical Monitor Name and Contact Information will be provided separately

Sponsor Serious Adverse Events (SAE) Contact Information: Refer to Safety Management Plan (SMP)

Regulatory Agency Identifying Number(s): EudraCT number 2022-000754-29

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

_____

_____ _____

Date

Investigator Signature

_____ _____

STUDY ADVISORY COMMITTEE

N/A

3. ABSTRACT

Title

Prospective cohort study to monitor the emergence of SARS-CoV-2 spike viral variants in immunocompromised non-hospitalised patients exposed to sotrovimab in Great Britain: LUNAR study

Rationale and background

Sotrovimab was granted a conditional marketing authorisation for the treatment of early coronavirus disease 2019 (COVID-19) infection in Great Britain (GB) on December 01, 2021. Sotrovimab is an early treatment that will be prescribed to patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who are at risk to progress to severe disease in non-hospitalised settings. There is a theoretical risk of monoclonal antibodies selecting for viral variants which could have the potential for increased transmissibility and/or reduced susceptibility to sotrovimab or to vaccine-derived immunity. Immunocompromised (IC) patients, who are on a prioritised list to receive treatment should they become infected, present a particular risk for variants because of their potential for prolonged viral shedding, and thus, present a risk for the emergence of mutations and potential onward community transmission.

This genomic surveillance study will aim to describe changes in the SARS-CoV-2 spike protein observed in IC patients receiving sotrovimab in sentinel sites at a national level to assess potential emergence of viral variants.

Research question and objective(s)

Amongst IC non-hospitalised patients treated with sotrovimab as part of standard clinical care:

Primary Objectives:

1. Evaluate the proportion of patients eligible for sequence analysis that have any amino acid (AA) change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days)

2. Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days)

Secondary Objectives:

1. Evaluate the proportion of patients eligible for sequence analysis with variants of concern (VOC) and under investigation (VUI) on the earliest possible sample including baseline

2. Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by reverse transcriptase polymerase chain reaction (RT-PCR)

3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, intensive care unit [ICU] admission and death) through Day 28 post sotrovimab administration

4. Describe AA (detected at >5% allelic frequency) changes in SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay

5. Describe AA changes in the consensus sequence (>50%) of SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads below the threshold for detection of AA changes at >5% allelic frequency but with sufficient levels to generate consensus sequencing data

Study design

Prospective cohort study

- Non-hospitalised patients who are being treated with sotrovimab as part of standard of clinical care will be screened and enrolled if eligible (Day 0 = baseline). Informed consent, patient characteristics (demographic and clinical), and treatment history (related to COVID-19 and underlying diseases) will also be recorded at Day 0.
- Baseline nasal/oropharyngeal swab sample will be collected on site, as per protocol, under supervision after training and sent to the central analytical laboratory.
- Follow-up nasal/oropharyngeal swab samples (Day 7, 14 and 28 (+/-2 days)) will be collected by the patients using home test kits or by healthcare professionals (HCP) in case of hospitalisation, as per protocol, with samples sent to the central analytical laboratory.
- Sequencing analyses will be conducted on all SARS-CoV-2 positive nasal/oropharyngeal swab samples that meet the threshold criteria for the sequencing assay.

Population, including the setting and study population

Inclusion criteria:

1. Adult patients ≥18-year-old
2. IC (as defined in the clinical commissioning policy [NHS England, 2022])
3. A positive PCR or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management
4. Prescribed treatment with sotrovimab as standard of clinical care
5. Able to provide informed consent and willing to adhere to study-related procedures

Exclusion criteria:

1. Patients who require hospitalisation (related or not to COVID-19) at baseline
2. Patients who initiated sotrovimab therapy in in-patient settings
3. Patients unable to perform follow-up sample collection

4. Blinded patients from other COVID-19 related trials

From the Clinical Commissioning Policy, the following groups will also be excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria not listed below [NHS England, 2022]*:*

5. Cohort of patients with rare neurological conditions
6. Cohort of patients with Down's syndrome
7. In the cohort of patients with renal disease::
    - Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression (patients with renal disease cohort)
8. In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), class B or class C (decompensated liver disease)

The decision to treat patients with sotrovimab will be made prior to and independently from the decision to enroll patients into the study by the patient's healthcare team. This is to ensure that sotrovimab is prescribed as per standard of clinical care. The patient will then be screened and enrolled in the study with informed consent and baseline sample collection taken prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). A patient who declines to be enrolled in the study will still receive sotrovimab when eligible for the treatment.

Variables (for primary and secondary objectives)

- Exposure: Sotrovimab administration
- Primary endpoint:
    - Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 1)
    - Proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 2)
- Secondary endpoints:
    - Proportion of patients eligible for sequence analysis with VOC and VUI on the earliest possible sample including baseline (Secondary Objective 1)
    - Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2)
    - Clinical outcomes at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 3):
        - Proportion of patients that are admitted to hospital for any cause and for COVID-19 reasons
        - Proportion of patients requiring new or increased oxygen support

  - Proportion of patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
  - Proportion of all cause ICU admission
  - Proportion of all cause deaths and COVID-19 related deaths
- AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay (Secondary Objective 4)
- AA changes in the SARS-CoV-2 spike consensus sequences from baseline in samples where viral load is insufficient for >5% allelic frequency analysis but sufficient to generate consensus level sequencing data (Secondary Objective 5)

Covariables:

Patient characteristics measured at baseline (demographics, number of days of COVID-19 symptoms (if symptomatic) and number of days since initial COVID-19 positive test result at time of receiving treatment, co-morbidities including immunocompromising condition, treatment history including immunosuppressant treatment, previous SARS-CoV-2 infections, COVID-19 vaccination status, serostatus if available, other treatment for COVID-19 including antivirals or other monoclonal antibodies).

Data sources:

After obtaining informed consent, inclusion/exclusion and baseline patient characteristics and treatment history data will be collected and documented. Any adverse event (AE) (serious and non-serious) observed during sotrovimab treatment (e.g., infusion-related reaction) and considered related to sotrovimab will be collected. Completion of baseline nasal/oropharyngeal sample collection and dispensing of at home lab kits to the patient will be completed and documented prior to patient discharge. Any baseline patient characteristics or treatment history unable to be collected during the baseline visit can be collected retrospectively from the patient or the patient's regular HCPs during the follow up period. Patients will receive a phone call at Day 7, 14 and 28 (+/- 2 days) to collect follow-up clinical outcomes and safety information (AEs) with a reminder for completion of at home nasal/oropharyngeal sample collection at the required timepoints. Participating sites may also contact patient's regular HCPs for clinical outcomes and safety information data as required. All baseline and follow-up data will be recorded in the electronic case report form (eCRF).

Virology data will be reported following the central analytical laboratory analysis of baseline, day 7, 14 and day 28 (+/-2 days) nasal/oropharyngeal samples as detailed in the statistical analysis plan (SAP).

Study size:

As a sentinel surveillance study, the aim will be to set up approximately 10 sites that are geographically spread across all 3 GB countries and collect data from a target of 500 (up to 625) patients over the course of a year. Flexible enrolment caps per site and per month may be considered. The aim is to ensure continuous enrolment with appropriate

geographical representation over the 12-month study period to reflect the fast-evolving COVID-19 pandemic. In addition, the target sample size will be re-assessed after the first 200-300 patients are enrolled in regard to progression towards achieving the primary objective, with the potential to decrease or increase the target number accordingly.

Data analysis:

Essential analyses

- Sequencing of samples on a regular basis (as detailed in the study laboratory manual) is required.
    - For patients eligible for sequencing analysis, proportion of patients with AA change from baseline in the epitope of sotrovimab (Primary Objective 1)
    - For patients eligible for sequencing analysis, proportion of patients with AA change from baseline in the spike protein (Primary Objective 2)
    - For samples with viral load above the threshold for allelic frequency determination, AA changes in SARS-CoV-2 spike protein at >5% allelic frequency compared to baseline will be reported as described in the SAP (Secondary Objective 4)
    - For samples with viral load below the threshold for low (5%) allelic frequency analysis, but above the threshold for consensus sequence generation, AA changes in the SARS-CoV-2 spike protein consensus sequence from baseline will be reported as described in the SAP (Secondary Objective 5)
- For patients eligible for sequencing analysis, VOC, VUI and other lineages information as classified by UKHSA (United Kingdom Health Security Agency) and WHO (World Health Organization) will be identified from sequencing data (Secondary Objective 1)
    - This analysis will be done on the earliest possible sample and reported only once per patient as described in the SAP
- Comorbidities, clinical outcomes, patients with undetectable virus and safety events data will be described and reported with counts and proportions (Secondary Objective 2 and 3).

Exploratory analyses

1. Describe viral characteristics (e.g. viral load, VOC/VUI, AA changes) in patients who subsequently require hospital admission or die due to COVID-19 post sotrovimab treatment
2. Establish whether changes in AA from baseline identified in the SARS-CoV-2 spike protein are reported sequences in genomic databases (e.g. Global initiative on sharing all influenza data [GISAID])

Milestones:

Actual Study Start: First Patient First Visit – 21 June 2022
Estimated Study End: Last Patient Last Visit – 20 July 2023

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	03 May 2022	Abstract, Section 8.1 Table 1 Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections. "The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab **or as close as possible to the end of sotrovimab infusion**"	The Ethics committee requested more time for patients to review and sign the ICF. To avoid any delay in sotrovimab administration, it was agreed to collect the baseline nasal/oropharyngeal swab just after sotrovimab infusion if it is not possible to collect before. By allowing for the baseline sample to be collected soon after infusion, the patient will have additional time to evaluate their participation whilst still enabling a viable sample to be collected.
2	03 May 2022	Abstract and Section 5 Milestones	The text in bold was updated in the appropriate section: Estimated Study Start: First Patient First Visit **– 21 June 2022** Estimated Study End: Last Patient Last Visit **– 20 July 2023** Start of data collection: Estimated **June 2022** End data collection: Estimated **July 2023** Final report of study results: Estimated **November 2023**	The study start has been delayed and new timelines are now proposed in the amendment

3	20 January 2023	PASS information	The ATC code for sotrovimab, J06BD05, was added	Addition of ATC code
4	20 January 2023	PASS information	Correction of a formatting error that truncated secondary objective 5 in the section Research question and objectives	Correction following authority comment
5	20 January 2023	Abstract, Section 8.1 Table 1 Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab **or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion)**"	Clarification of how long after the end of sotrovimab infusion the baseline swab can be taken
6	20 January 2023	Section 8.1 Table 1 Schedule of Activities, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "Persistent positive results will be reported back to the sites **upon site request** (as described in the study reference manual)."	Preference of sites
7	20 January 2023	Section 5 Milestones, Section 8.7.4 Interim Analysis	An interim analysis assessing the primary and secondary objectives was added	Health authority request
8	20 January 2023	Section 8.2 Study Population and Setting	Text in ~~strikethrough~~ was deleted: "It will be conducted for a period of 12 months in approximately 10 sites ~~selected following feasibility assessment from the list of COVID Medicine~~	Delivery of COVID-19 therapeutics to non-hospitalised patients is expected to become part of routine NHS services from April 2023 (https://www.england.nhs.uk/coronavirus/wp-

			~~Delivery Units (CMDUs [https://www.england.nhs.uk/coronavirus/publication/covid-medicine-delivery-unit-directory/])~~ in GB, or until the enrollment of 500 (up to 625) patients is met, or until sotrovimab is no longer used in GB, whichever comes first."	content/uploads/sites/52/2022/12/C1677-commissioning-framework-covid-19-therapeutics-for-non-hospitalised-patients.pdf)
9	20 January 2023	Abstract, Section 8.4 Data sources, Section 8.7.1.1 Primary objective, Section 8.7.1.2 Secondary objective, Section 8.7.3 General considerations for data analyses, Section 8.9 Limitations of the research methods	The term "reporting plan" was replaced with "statistical analysis plan"	The statistical analysis plan contains all details about what the study will report
10	20 January 2023	Abstract, Section 8.7.2 Exploratory Analyses	The third exploratory analysis was removed: "3. Explore the feasibility of linkage with routinely collected samples (as per standard of clinical care) for spike protein monitoring in patients who remain SARS-CoV-2 positive beyond 28 days as part of a longer follow-up for this sub-population"	Exploratory analysis no longer relevant and not feasible
11	20 January 2023	Abstract, Section 8.1 Study	The reference "MHRA. Central Alert System CAS-ViewAlert. Antivirals or	Updated recommendations for antiviral treatment in

		Design, Section 8.2.1 Inclusion criteria, Section 8.2.2 Exclusion criteria, Section 10 References	neutralising monoclonal antibodies (nMABs) for non-hospitalised patients with COVID-19 . 27 January 2022. CAS-ViewAlert (mhra.gov.uk)" was replaced with "NHS England. Coronavirus » Interim Clinical Commissioning Policy: Treatments for non-hospitalised patients with COVID-19. 28 November 2022"	non-hospitalised patients with COVID-19
12	20 January 2023	Section 6.1 Background, Section 10 References	The reference to the Summary of Product Characteristics for Xevudy (MHRA, 2021) was updated to GlaxoSmithKline UK, 2022	Updated version of Summary of Product Characteristics
13	20 January 2023	Throughout protocol	Minor corrections to punctuation have been made throughout the protocol	Administrative changes

5. MILESTONES

Milestone	Planned date
Start of data collection	June 2022
End of data collection	Estimated July 2023
Interim report of study results	Q2 2023
Registration in the EU PAS register	March 2022
Final report of study results	Estimated November 2023

6. RATIONALE AND BACKGROUND

6.1. Background

The novel beta-coronavirus SARS-CoV-2 (Coronavirus disease 2019 [COVID-19]) was first detected in December 2019, with initial reports of its emergence in Wuhan, China. Since this time, the virus, which can cause severe pneumonia in infected individuals, has spread throughout the world, causing unprecedented impacts on health, economy, and social security [Wu Z, 2020].

The spectrum of symptomatic COVID-19 ranges from mild disease without pneumonia to critical disease requiring hospitalisation with intensive care unit (ICU) care. As of 18 February 2022, approximately 18.5 million cases (people who have had at least one positive COVID-19 test result) and approximately 181,424 COVID-19 deaths have been recorded in the United Kingdom (UK) [GOV.UK, 2022]. The risk of hospital admission for a person detected as a case of Omicron appears to be reduced compared to a case of Delta [UKHSA, 2022].

COVID-19 vaccination remains the foundation for SARS-CoV-2 control, and vaccine effectiveness has reduced the magnitude of hospitalisations and deaths despite continued high viral circulation [Lopez Bernal J, 2021a; Lopez Bernal J, 2021b]. More than 48 million people in the UK have received at least two doses of vaccine and about 38 million have received a booster/third dose [GOV.UK, 2022]. Nonetheless, vaccine immunogenicity and effectiveness are lower in certain high-risk groups such as those with immunocompromising conditions [Chodick, 2021; Embi, P. J, 2021].

Sotrovimab (VIR-7831; GSK4182136) is a human neutralising anti-SARS-CoV-2 antibody which contains a 2 AA Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. Sotrovimab binds to a conserved epitope on the SARS-CoV and SARS-CoV-2 spike protein outside the receptor-binding motif and has been shown to neutralise pseudovirus and live virus in several independent laboratories [Pinto, 2020]. This unique binding site may retain activity against emerging SARS-CoV-2 variants that may be resistant to other mAbs [Wang, 2021]. COMET-ICE, a randomised, double-blind, multi-centre, placebo-controlled trial of sotrovimab for the early treatment of COVID-19 in non-hospitalised patients, demonstrated 79% reduction in disease progression to hospitalisation or death

among patients treated with sotrovimab compared with placebo [Gupta A, 2021]. This single pivotal study supported the Marketing Authorisation Application (MAA) in Great Britain (GB).

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a conditional marketing authorisation for sotrovimab for the treatment of people with mild to moderate COVID-19 who are at high risk of developing severe disease [GlaxoSmithKline UK, 2022]. The final summary data on England's shielding list issued at the end of September 2021, showed that about 3.7 million individuals were included as being at highest risk for severe COVID-19, or about 6.5% of the population [NHS Digital, 2021; Office for National Statistics, 2021; Hippisley-Cox J, 2021]. Immunocompromised (IC) patients, a subset of the shielding list, are not only subject to increased risk of severe outcomes such as hospitalisation and mortality, but evidence also shows that this group are more likely to transmit the virus to their household contacts, leading to increased clusters of the virus. This population is also more likely to shed the virus for a longer duration, potentially increasing the risk of emergent variants [Lewis, 2021; Aydillo, 2020; Niyonkuru, 2021].

The impact of the recently detected Omicron variant on the effectiveness of vaccines and therapeutics is unknown pending further research, though very early findings suggest that the Omicron variant may have greater reinfection risk than Beta or Delta variants. *In vitro* studies of sotrovimab suggest that it retains antiviral activity against viral mutations in the spike proteins of Alpha, Beta, Gamma, Delta, Kappa, and Omicron BA.1 variants, whilst there is evidence of reduced antiviral activity of other currently authorised mAbs or vaccines [Torjesen, 2021; Pulliam, 2021; Cathcart, 2022]. In February 2022, GSK submitted preliminary *in vitro* data on the antiviral activity of sotrovimab against the BA.2 variant to the MHRA. These data are currently under assessment. GSK will provide all new relevant *in vitro* data on the variants of concern (VOC) and variants under investigation (VUI) of SARS-CoV-2 to the MHRA (UK). The protocol will not be updated for each new VOC or VUI, but GSK *in vitro* data will be published contemporaneously (e.g. in the Cathcart et al pre-print [Cathcart, 2022]).

The epitope to which sotrovimab binds is comprised of 23 AAs. Amino acids comprising the epitope are highly conserved with >99.68% conservation among >5,500,000 spike sequences from SARS-CoV-2 deposited in the GISAID database as of 15 December 2021 (https://www.gisaid.org). In vitro pseudotyped virus assessment shows that the epitope sequence polymorphisms P337H/K/L/R/T and E340A/K/G/Q/V confer reduced susceptibility to sotrovimab [Cathcart, 2022].

Sotrovimab is thus a potentially critical therapeutic in the fight against COVID-19, for which there remains a high unmet medical need despite the recent success of preventative measures such as vaccines. Challenges with access to vaccines, vaccine hesitancy, medical contraindications to vaccines, IC individuals who may not respond to a vaccine, and importantly, the potential emergence of variant viruses that escape vaccine-derived immunity, will all contribute to what is likely to be an unfortunately large and enduring number of COVID-19 cases in need of treatment.

IC individuals have been shown to be at higher risk of breakthrough infections and are at higher risk for hospitalisation and death despite high vaccine uptake [Di Fusco, 2021; Hippisley-Cox J, 2021]. The same immune deficiencies that may predispose patients to severe COVID-19 outcomes can also result in a failure to mount robust immunity to SARS-CoV-2 following vaccination, which is why it is likely that IC patients will highly benefit from sotrovimab administration [Kearns, P, 2021; Mahase, 2021; NHS England, 2022; NICE, 2021].

6.2. Rationale

Since December 2020, a number of variants of SARS-CoV-2 have emerged globally, with a high level of uncertainty around their transmissibility, severity and potential for evading vaccine-induced immunity or developing resistance against antivirals and mAbs. SARS-CoV-2 variants can undergo mutations that alter the AAs in the spike protein of the virus [Harvey W.T, 2021]. In the UK, many of these variants have been detected and have since remained under surveillance by UKHSA through routine surveillance [UKHSA, 2021]. Variants may be designated as VOC or VUI, depending on the evidence at the time of their discovery.

Sotrovimab is an early treatment that will be prescribed to SARS-CoV-2 patients at risk to progress to severe disease in non-hospitalised settings. There is a theoretical risk of monoclonal antibodies selecting for viral variants which could have the potential for increased transmissibility and/or reduced susceptibility to sotrovimab or to vaccine-derived immunity. IC patients, who are on a prioritised list to receive treatment should they become infected, present a particular risk for variants because of their potential for prolonged viral shedding, and thus, present a risk for the emergence of mutations and potential onward community transmission.

Thus, this genomic surveillance study will aim to describe changes in the SARS-CoV-2 spike protein observed in IC patients receiving sotrovimab in sentinel sites at a national level to assess potential emergence of viral variants.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Amongst IC non-hospitalised patients treated with sotrovimab as part of standard clinical care:

7.1. Primary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days)
2. Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days)

7.2. Secondary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis with VOC and VUI on the earliest possible sample including baseline
2. Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by RT-PCR
3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, ICU admission and death) through Day 28 post sotrovimab administration
4. Describe AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay
5. Describe AA changes in the consensus sequence (>50%) of SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads below the threshold for detection of AA changes at >5% allelic frequency but with sufficient levels to generate consensus sequencing data

8. RESEARCH METHODS

8.1. Study Design

This study is a prospective cohort study (Figure 1).

This study will enrol IC non-hospitalised patients aged ≥18-year-old infected with SARS-CoV-2 and receiving sotrovimab treatment as per standard of clinical care for COVID-19 in selected facilities. Patients who require hospitalisation for COVID-19 are currently not eligible to receive sotrovimab [NHS England, 2022] and will be excluded; there is other ongoing research that will evaluate this population if sotrovimab is administered to this patient population. Patients prescribed sotrovimab who were hospitalised for non-COVID-19 reasons at baseline will also be excluded; this population being already eligible for other national genomic surveillance and requiring a different operational model. All participants that consent to be enrolled in the study will be followed up for up to 28 days post sotrovimab treatment. Patient and disease characteristics (e.g. demographics, number of days of COVID-19 symptoms (if symptomatic) and number of days since initial COVID-19 positive test result at time of receiving treatment, co-morbidities including immunocompromising condition and risk factors for COVID-19 progression, COVID-19 vaccination status, previous SARS-CoV-2 infection, serostatus if available) and treatment history (e.g. immunosuppressant treatment) will be collected at baseline (index date (D0), which corresponds to sotrovimab administration date). Other treatments for COVID-19 including antivirals or other monoclonal antibodies will be collected at baseline and follow-up if any.

Nasal/oropharyngeal samples for virological analysis will be collected at baseline and at three follow-up time points (Day 7, 14 and 28 (+/-2 days)), as per protocol (see Table 1).

Patients will be asked to take a throat and nasal sample with the same swab at each follow-up time point.

Collected nasal mid-turbinate swabs have demonstrated comparable sensitivity and good viral load correlation to clinician collected nasopharyngeal swabs (considered as the gold standard) for COVID-19 detection [Kojima, 2021; Alemany, 2021]. While the nasal/oropharyngeal sample will be collected on site at baseline under supervision after training (as detailed in the study reference manual), home test kits will be provided to the patients with clear explanations on the appropriate technique to collect the follow-up samples as well as instructions for return to the central analytical laboratory. The patient's subject identification number must be present on each of the home test kits (follow guidance in the study reference manual) and checked by study research staff, when these are provided to the patient to take home. Collection of the follow-up samples may also be performed by an HCP in case of hospitalisation. Home test kits are proposed to minimise patients' exposure to healthcare settings that in-person visits would require and to improve patient adherence to study-related procedures and follow up. All the samples will be sent to a central analytical laboratory for testing (i.e., viral load, and sequencing analyses amongst SARS-CoV-2 positive samples with sufficient viral load) (see Section 8.3.2).

Select key clinical outcomes data (e.g. hospital admission, respiratory support, ICU admission and death) will be collected at Day 7, 14 and 28 (+/-2 days) and documented in the eCRF. Phone calls to the patients by the study research staff will be planned at these three follow-up time points with the aim to complete the eCRF and to remind the patients to collect their follow-up nasal/oropharyngeal sample.

Table 1 Schedule of Activities

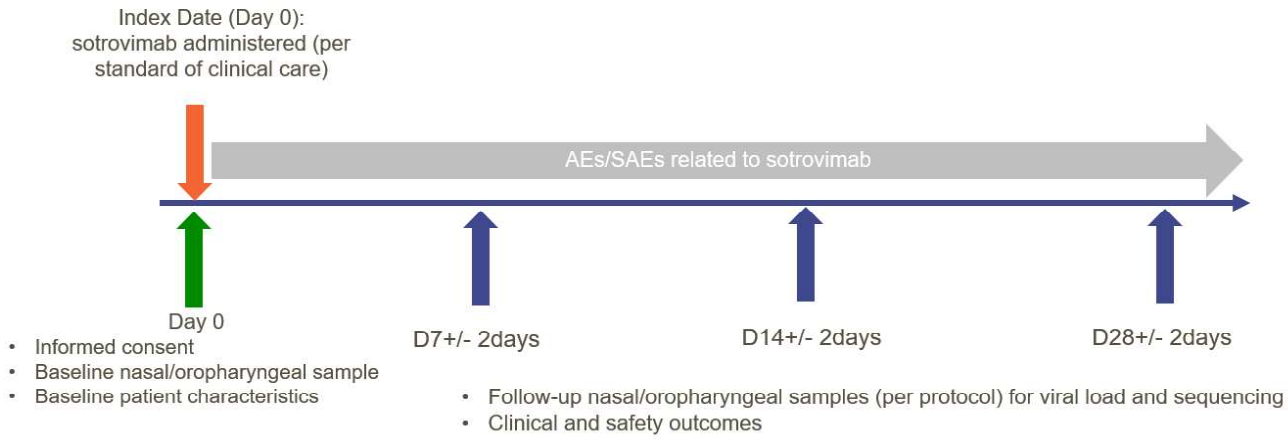
	Baseline **(Day 0, sotrovimab index date)**	**Follow Up Call 1** **(Day 7 ± 2)**[p]	**Follow Up Call 2** **(Day 14 ± 2)**[p]	**Follow Up Call 3** **(Day 28 ± 2)**[pq]
Pre-screening[a]	√			
Confirmation of sotrovimab prescription[b]	√			
Informed Consent [c]	√			
Eligibility confirmation[d]	√			
Enrolment[e]	√			
Nasal nasal/oropharyngeal swab	√ [f]	√[g]	√[g]	√[g]
Sotrovimab administration[h]	√			
Demography[i]	√			
Co-morbidities[j]	√			
Disease characterisation[k]	√			
Concomitant medications[l]	√	√	√	√
Vaccination status[m]	√	√	√	√
Clinical Outcomes[n]		√	√	√
Adverse events related to sotrovimab treatment[o]	√	√	√	√

[a] Pre-screening of potential patients is encouraged to make the eligibility and consent process as efficient as possible and reduce delay to sotrovimab administration.
[b] Evidence that the decision to administer sotrovimab was taken prior to consenting the patient to join the study must be documented in the patient's medical records.
[c] Informed consent must be taken prior to any study specific procedures being conducted with the patient.
[d] Evidence that all inclusion and no exclusion criteria have been met must be documented in the patient's medical records prior to enrolment.
[e] Register patient in EDC (Electronic Data Capture) system. Assign subject identification number to patient and document on enrolment log and patient materials (ICF [Informed consent form], contact card) and sample collection kits.
[f] The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). Patients must be trained in the self-administration of nasal/oropharyngeal swabs at baseline to support sample collection at follow up timepoints. Three sample collection kits must be provided to the patient for at home sample collection at follow up timepoints, staff must ensure correct subject identification number is present on each kit.

[g] Nasal/oropharyngeal swabs at follow up timepoints will be self-administered by the patient or HCP in case of hospitalisation. Samples must be returned to the central analytical laboratory by post as soon as practically possible. Use of priority post boxes is encouraged to ensure samples reach the central analytical laboratory within the analysis window.
[h] Sotrovimab administration is to be performed as per local standard of care and is not part of this study protocol.
[i] Demographic data including age (year and range), sex, smoking status, ethnicity and BMI (range) to be collected and documented in the patient's medical records.
[j] Refer to Section 8.3.3.1for list of relevant co-morbidities. Co-morbidities should be documented in the patient's medical record at baseline.
[k] Disease characterisation data including duration of COVID-19 symptoms (days), previous SARS-CoV-2 infection and serostatus (if available) to be collected at baseline and documented in the patient's medical records.
[l] Concomitant medications, both related to and non-related to SARS-CoV-2 infection, must be collected at baseline and during follow up calls and must be documented in the patient's medical.
[m] COVID-19 vaccination status, including number of vaccinations, date (month) and brand, must be collected at baseline and during follow up calls and documented in the patient's medical record.
[n] Clinical outcomes including hospital admission, respiratory support, ICU admission and death will be collected and recorded in the patient's medical records during follow up calls.
[o] Refer to Section 11.3 for details on safety events to be reported.
[p] Patients who progress to severe disease and may require COVID-19 related hospitalisation should be actively contacted and followed-up where possible by site staff to obtain samples and follow up data as per protocol.
[q] Patients with a persistent positive sample at the end of the 28 day follow up period will have their positive results reported back to the sites upon site request (as described in the study reference manual).

Patients who progress to severe disease and may require COVID-19 related hospitalisation will be actively contacted and followed-up where possible by the study research staff from the site where sotrovimab was administered. They or HCPs involved in the patient's clinical care may collect samples whilst the patient is hospitalised. Patients will be given a contact card and asked to notify the site if they cannot be contacted for the follow-up calls. To reduce loss to follow up of hospitalised patients, preference will be given to sites where it is likely that patients who require hospitalisation following enrolment will be readmitted to the study site. This will be assessed as part of site feasibility.

Figure 1 Study Design



8.2. Study Population and Setting

This post approval study will aim to start as soon as possible since sotrovimab is now deployed in GB (England, Scotland, Wales). It will be conducted for a period of 12 months in approximately 10 sites in GB, or until the enrollment of 500 (up to 625) patients is met, or until sotrovimab is no longer used in GB, whichever comes first. The aim will be to identify sites that are geographically spread across all three of the home nations. Preference will be given to sites where it is likely that patients who require hospitalisation following enrolment will be readmitted to the study site. Another key factor considered when selecting study sites will be the capacity to start the study quickly, from both a staffing and governance perspective.

This study is intended to cover a fixed period of vulnerability when a limited number of drugs and vaccines are available to generate evidence to understand the risk of variant emergence. UKHSA may continue to monitor the evolving variants and their impact on COVID-19 therapeutic and vaccine effectiveness as part of their routine surveillance activity.

8.2.1. Inclusion Criteria

1. Adult patients aged ≥18 years
2. IC (as defined in the clinical commissioning policy [NHS England, 2022])
3. A positive PCR or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management
4. Prescribed treatment with sotrovimab as standard of clinical care
5. Able to provide informed consent and willing to adhere to study-related procedures

The list of IC population eligible to receive sotrovimab will be derived from the IC cohorts outlined in the interim Clinical Commissioning Policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs [NHS England, 2022]. The list may include specific IC patients within the following cohorts:

- Patients with a solid cancer
- Patients with a haematological disease and stem cell transplant recipients
- Patients with renal disease
- Patients with liver disease
- Patients with immune-mediated inflammatory disorders (IMID)
- Immune deficiencies
- HIV/AIDS
- Solid organ transplant recipients

Of note, the criteria for the IC cohorts are subject to change as they will follow the latest NHS guidance. The protocol will not be amended to accommodate updates to MHRA guidance, but the criteria will be updated accordingly in the study reference manual.

The decision to treat patients with sotrovimab will be made prior to and independently from the decision of enrolling patients into this study by the patient's healthcare team. Informed consent form and baseline sample collection will be taken prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). This study will therefore include patients who have received sotrovimab dosed as part of their standard clinical care

8.2.2. Exclusion Criteria

1. Patients who require hospitalisation (related or not to COVID-19) at baseline
2. Patients who initiated sotrovimab therapy in inpatient settings
3. Patients unable to perform nasal/oropharyngeal sample collection
4. Blinded patients from other COVID-19 related trials

From the Clinical Commissioning Policy, the following groups will also be excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria not listed below [NHS England, 2022]*:*

5. Cohort of patients with rare neurological conditions
6. Cohort of patients with Down's Syndrome
7. In the cohort of patients with renal disease:
    - Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m^2) without immunosuppression (patients with renal disease cohort)
8. In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), Child's-Pugh class B or C (decompensated liver disease)

8.3. Variables

8.3.1. Exposure Definitions

Sotrovimab Xevudy^{TM}, dose and administration per standard of clinical care

8.3.2. Outcome definitions

8.3.2.1. Primary Endpoint (Primary Objective)

1. Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 1)
2. Proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 2)

Laboratory process

Samples will be dispatched by sites (baseline sample) and patients or HCPs if patients are hospitalised (follow-up samples) to a central analytical laboratory which will follow its own procedures for sequencing techniques.

Sequence analysis of the SARS-CoV-2 spike gene will be attempted on swab samples from all participants eligible for sequence analysis. Viral load will also be measured for all samples. Changes in the spike protein that arise following treatment will be determined by comparing baseline and post-baseline sequencing data for a given patient. More detailed information will be available in the overarching study laboratory manual.

8.3.2.2. Secondary Endpoints

1. Proportion of patients eligible for sequence analysis with SARS CoV-2 VOC or VUI on the earliest possible sample (Secondary Objective 1)
    - Variant identification, pango lineage and AA changes in VOC and VUI in addition to their defining mutations will be reported
2. Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2)
3. Clinical outcomes through Day 28 post sotrovimab treatment (Secondary Objective 3):
    - Proportion of all cause hospital admissions and related to COVID-19
    - Proportion of patients requiring new or increased oxygen support (supplemental oxygen [not high flow], non-invasive ventilation or high-flow, invasive mechanical ventilation or Extracorporeal membrane oxygenation [ECMO])
    - Proportion of all cause ICU admissions
    - Proportion of all cause deaths and COVID-19 related deaths
4. AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay (Secondary Objective 4)
5. AA changes in the SARS-CoV-2 spike consensus sequences from baseline in samples where viral load is insufficient for >5% allelic frequency analysis but sufficient to generate consensus level sequencing data (Secondary Objective 5)

Of note, exploratory endpoints will be defined and pre-specified in the statistical analysis plan (SAP).

8.3.3. Confounders and Effect Modifiers

8.3.3.1. Patients Characteristics

Demographic (at baseline)

- Age (year)
- Age range: 18-64; 65-74; 75-84; ≥85
- Sex

- Current smoking status (Yes = current smoker, No = ex-smoker, never smoker),
- Ethnicity
- Body mass index (BMI) (kg/m2): <18.5; 18.5-24.9; 25-29.9; 30-34.9; 35-39.9; ≥40

Comorbidities (at baseline) see Section 8.4 for data source and collection

- Immunocompromising condition
    - The specific conditions will be grouped by set of immunocompromising conditions for analytic purposes
- Obesity (BMI ≥ 30 kg/m^2) and overweight (BMI ≥ 25 kg/m^2)
- Cardiovascular disease (including congenital heart disease) or hypertension
- Cerebrovascular disease
- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Other chronic respiratory disease (moderate-to-severe), interstitial lung disease, cystic fibrosis and pulmonary hypertension
- Chronic kidney disease and stage
- Chronic liver disease
- Diabetes mellitus (DM)
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Pregnancy
- Sickle cell disease
- Having a medical-related technological dependence (e.g. tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])
- Other

Disease characteristic (at baseline)

- Duration of COVID-19 symptoms (days) prior to receiving sotrovimab
- Previous SARS-CoV-2 infection
- Serostatus, if available, test used (i.e. assay manufacturer; test for antibodies to spike protein or test for nucleocapsid protein or other) and date

Co-medication (data collected at baseline and follow-up time points)

- Related to SARS-CoV-2 infection
    - Corticosteroids (inhaled, systemic)
    - Remdesivir
    - IL-6 inhibitors
    - Other mAbs (casirivimab and imdevimab, or other agents if licensed during the study period)
    - Antivirals (molnupiravir, nirmatrelvir and ritonavir, other)
    - Others following national guidance
    - Experimental drugs

- Non-related to SARS-CoV-2 infection (e.g. immunosuppressant treatment)

COVID-19 vaccination status (data collected at baseline and follow-up time points)

- Number of vaccinations, date (month) and brand of each vaccination

8.4. Data Sources

After obtaining informed consent, inclusion/exclusion and baseline patient characteristics and treatment history data will be collected and documented. Any initial AEs observed during sotrovimab treatment (e.g., infusion-related reaction), completion of baseline nasal/oropharyngeal sample and dispensing of at home lab kits to the patient will be completed and documented prior to patient discharge. Any baseline patient characteristics or treatment history unable to be collected during the baseline visit can be collected retrospectively directly from the patient or the patient's regular HCPs during the follow up period. Patients will receive a phone call at Day 7, 14 and 28 (+/- 2 days) to collect follow-up clinical and safety outcomes information, any new or changes in co-medications/ vaccination status, with a reminder for completion of at home nasal/oropharyngeal sample collection at the required timepoints. Participating sites may also contact patient's regular HCPs for clinical and safety outcomes data as required. All baseline and follow-up data will be recorded in the eCRF.

Virology (viral load and viral sequencing) data will be reported following the central analytical laboratory analysis of baseline, day 7, 14 and day 28 (+/-2 days) nasal/oropharyngeal samples as detailed in the SAP.

(For patients progressing to severe COVID-19 and being hospitalised – see Section 8.1)

8.5. Study Size

The primary endpoints are the proportion of patients eligible for sequence analysis that have any AA change from baseline i) in the epitope of sotrovimab binding and ii) in the spike protein at Day 7, 14 and 28 (+/-2 days). The AA changes from baseline in the spike protein will be submitted to MHRA at the individual-patient level as part of ongoing surveillance reporting. Precision around the estimates of the primary endpoints will help to define the target sample size. No prior information about these precise endpoints is available, and the closest comparable available data are derived from the COMET-ICE clinical trial (i.e. conducted in immunocompetent patients with co-morbidities). Preliminary analyses of these sequencing data reported:

- The percentage of sotrovimab treated patients that had treatment emergent AA changes detected **in the epitope of sotrovimab binding** at the consensus sequencing level was approximately 20% (when emergent changes were defined at 5% allelic frequency), and approximately 9% (when defined at 15% frequency)
- The percentage of sotrovimab treated patients that had emergent AA changes more broadly **across the spike protein** was approximately 80% and 52% (defined at 5% and 15% allelic frequency respectively).

A higher prevalence is expected in IC patients.

Precision calculations based on this information, and some additional values, are presented below (output from the software PASS (NCSS, LLC, Version 19.0.1). They show that, for example:

- If 50% of patients with AA changes that meet the criteria for the variable of interest (i.e. the estimated percentage that gives the widest confidence interval (CI)) is observed, then a sample size of 500 patients will give reasonable precision around the estimate (95% CI 45.5%-54.5%).
- If 9% of patients that meet the criteria is observed, a target sample size of 500 patients will also yield reasonable precision around the estimate (95% CI 6.7%-11.9%).

Table 2 Numerical Results for Two-Sided Confidence Intervals for One Proportion – Confidence Interval Formula: Score with Continuity Correction [Fleiss, 2003; Newcombe, 1998]

Confidence Level	Sample Size (N)	Actual Width	Proportion (P)	Lower Limit	Upper Limit
0.950	500	0.041	0.050	0.033	0.074
0.950	500	0.052	0.090	0.067	0.119
0.950	500	0.055	0.100	0.076	0.131
0.950	500	0.078	0.250	0.213	0.291
0.950	500	0.089	0.500	0.455	0.545
0.950	500	0.089	0.520	0.475	0.564
0.950	500	0.072	0.800	0.762	0.834
0.950	500	0.065	0.850	0.815	0.880

- Confidence level is the proportion of cIs (constructed with this same confidence level, sample size, etc.) that would contain the population proportion.
- N is the size of the sample draw from the population.
- Width is the distance from the lower limit to the upper limit.
- Actual width is the value of the width that is obtained from the procedure.
- Proportion (P) is the assumed sample proportion.
- Lower Limit is the lower limit of the CI.
- Upper Limit is the upper limit of the CI.

Using an estimate of 20% of patients being lost to follow-up, the plan will be to increase recruitment up to 625 patients to meet the target sample size of 500. It is also anticipated that in some patients, the viral load in samples collected at days 7, 14, and 28 (+/-2 days) will be too low for determination of the variable of interest. While undetectable viral load is a goal for treatment, this would further reduce the number of patients contributing to the assessment of the primary endpoint. Nonetheless, there remains adequate precision if

there are fewer patients contributing to analyses at day 7, for example (e.g. if there were 400 patients with a detectable viral load and 50% had AA changes that meet the criteria of interest, then the precision would be 95% CI 45.0-55.0%).

As a sentinel surveillance study, the aim will be to collect 500 (and up to 625) patients over the course of a year across the GB to meet the target sample size. Flexible enrolment caps per site and per month may be considered. The aim is to ensure continuous enrolment with appropriate geographical representation over the 12-month study period, to reflect the fast evolving COVID-19 pandemic. In addition, the target sample size will be re-assessed after the first 200-300 patients are enrolled in regard to progression towards achieving the primary objective, with the potential to decrease or increase the target number accordingly.

8.6. Data Management

Data collection and data source is described in Section 8.4.

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan (DMP) or equivalent contract research organisation (CRO) document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations [CROs]).

More granular level process for data management will be described in the overarching study DMP.

8.6.1. Timings of Assessment during Follow-up

Patients will be followed for 28 days from the time they received sotrovimab treatment (index date (D0)) in one of the clinical sites. Data and samples will be collected following the schedule below (see also Table 1):

- Day 0 On-site screening:
    - Confirmation that decision to administer sotrovimab (per standard of clinical care) has been made by the treating HCP
    - Informed consent and enrolment
    - Baseline sample collection under supervision after training (nasal/oropharyngeal) prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion).

Data collection of patient and disease characteristics (e.g. demographic, medications and comorbidities) when possible
    - Three sample collection kits must be provided to the patient for home collection at each follow up timepoints (D7, D14, D28 [+/-2days]), with subject identification present on each kit (as per guidance in the study reference manual).
- Day 7 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0
- Day 14 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0
- Day 28 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0

For patients progressing to severe COVID-19 and being hospitalised – see Section 8.1.

The follow-up of patients with a persistent positive sample at the end of the study period (i.e. Day 28) is described in Section 8.7.2 as an exploratory analysis. Persistent positive results will be reported back to the sites upon site request (as described in the study reference manual).

8.7. Data analysis

8.7.1. Essential Analysis

This study is descriptive. Categorical variables will be described using counts, proportions and 95% CI and continuous variables will be described using measures of central tendency (e.g. mean, interquartile range, etc.)

8.7.1.1. Primary Objective

- Sequencing of samples on a regular basis (as detailed in the study laboratory manual) is required.
- The primary analysis of data will include:
    - Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding

- Proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein
- More details on any sub-analyses performed by sub-groups will be described in the SAP.

8.7.1.2. Secondary Objective

- VOC, VUI and other lineages information as classified by UKHSA and WHO will be identified from sequencing data for patients eligible for sequencing analysis (Secondary Objective 1)
    - This analysis will be done on the earliest possible sample and reported only once per patient as described in the SAP

- Comorbidities, clinical outcomes, patients with undetectable SARS-VoV-2 viral ribonucleic acid and safety events data will be described and reported with counts and proportions with a 95% CI (Secondary Objective 2 and 3).

- AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay (Secondary Objective 4)

- AA changes in the SARS-CoV-2 spike consensus sequences from baseline in samples where viral load is insufficient for >5% allelic frequency analysis but sufficient to generate consensus level sequencing data (Secondary Objective 5)

8.7.2. Exploratory Analysis

1. Describe viral characteristics (e.g. viral load, VOC/VUI, AA changes) in patients who subsequently require hospital admission or die due to COVID-19 post sotrovimab treatment

2. Establish whether changes in AA from baseline identified in the SARS-CoV-2 spike protein are reported sequences in the genomic databases (e.g. GISAID)

8.7.3. General Considerations for Data Analyses

More granularity for data analyses and reporting will be available in the overarching project SAP.

8.7.4. Interim Analysis

An interim analysis is planned to be conducted to support regulatory health authority post authorisation commitments. The analysis aims to assess the primary and secondary objectives and is due in Q2 2023. For details about the analysis refer to the SAP.

8.8. Quality control and Quality Assurance

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.8.5 for more details regarding the audit process.

8.8.1. Data Quality Assurance

Syneos Health and GSK are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained by the Site Management Associate (SMA) on the protocol, study logistics, and the EDC system.

Veeva Vault CDMS (Clinical Data Management System) will be the EDC system used to manage data collection during this study; it is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (*e.g.*, laboratory data). The investigator is responsible for ensuring prospective data is entered in a timely manner and verifying that data are accurate and correct by physically or electronically signing the eCRF. Guidance on completion of CRFs will be provided in the eCRF Guidelines.

On-line logic checks will be built into the EDC system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study site and answered electronically by the study site personnel.

8.8.2. Access to Source Data/Documents

The Investigator will allow Sponsor representatives, contract designees, authorised regulatory authority inspectors, and Independent Ethics Committee (IEC) to have direct access to all documents pertaining to the study.

8.8.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. All study materials will be returned to the Sponsor after the study has been completed.

Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations. According to International Council on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

8.8.4. Study Monitoring

Subject data will be monitored using a risk-based approach, with remote monitoring being preferred to reduce burden on sites. The monitoring strategy will be documented in the study Site Management (monitoring) Plan and will include flexibility in approach to account for COVID-19 restrictions that may change during the study.

8.8.5. Audits and Inspections

Responsible IEC/Competent Authority and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.9. Limitations of the Research Methods

Strengths of the proposed study include its prospective design, which provides clear temporal information, and use of advanced laboratory methods to describe AA changes in viral genetic sequence in an IC population that is at risk for both poor clinical outcomes and the development of novel substitutions, deletions or insertions in the spike protein of SARS-CoV-2 virus.

There are several limitations to the interpretation of the results of this study, summarised below:

Design

This surveillance study will aim to monitor the emergence of changes in spike protein over time following the administration of sotrovimab. The aim will be to monitor the changes in the entire spike protein, but some substitutions, deletions or insertions of concern may occur outside of the spike. All changes that are identified in the SARS-CoV-2 spike protein will be recorded and reported per the SAP.

Selection bias

Since patients who are hospitalised for non-COVID-19 reasons or who are unable to collect nasal/oropharyngeal swabs will be excluded, there is a possibility of selection bias in recruiting a somewhat healthier population. However, it is expected that the impact on the primary outcome will be minimal. Immunosuppressed status, regardless of hospitalisation status, should be the main factor impacting the AA changes in the spike protein. Since the study will enrol a range of highly IC patients, selection bias should be minimal.

Testing procedures

The baseline sample will be a nasal/oropharyngeal swab collected on site and supervised by a HCP, while pragmatic, patient-focused solutions will ask study participants to

collect their follow up samples at 7-, 14- and 28-days using home test kits. Study staff will not be able to verify whether samples are collected and handled properly, which may impact the sensitivity of subsequent sequencing testing of patient samples. However, this collection approach was weighed against asking COVID-19 positive, IC people having to seek testing outside their residence. Self-collected nasal/oropharyngeal swabs have demonstrated comparable sensitivity and good viral load correlation to clinician collected nasopharyngeal swabs (considered as the gold standard) for SARS-CoV-2 detection [Kojima, 2021; Alemany, 2021]. The patients will also be trained to increase chances of getting the appropriate samples. Finally, nasopharyngeal swabs generally should not be done in patients with significant thrombocytopenia or bleeding disorders, which some of this IC population would likely have.

Distribution of virus across the respiratory tract may vary between patients. Therefore, an infected patient may have detectable virus in sputum but not in nasal/oropharyngeal swabs. This limitation and the potential for false negative results when using nasal/oropharyngeal swabs are acknowledged. Regular re-assessments of the sample collection strategy to ensure the appropriate capture of the primary outcome will be planned.

Loss to follow up

Although the duration of follow up is relatively short (28 day +/- 2 days) all data will be collected remotely, and samples will be provided by post and relies on patient compliance with protocol procedures. It is expected that there may be challenges obtaining follow up information and samples from enrolled patients. Clinical sites will proactively contact patients on at least 3 occasions over a period of 4 days (+/- 2 days from expected date) in order to reduce loss to follow-up. Reasons for loss-to-follow-up will be recorded in the eCRF if available. Attempts will also be made by the study staff to contact or follow-up patients if they are admitted to the hospital.

In evaluating clinical outcomes and safety events at later time points, it is possible that loss to follow up will be differential, with patients experiencing adverse clinical outcomes or safety events either more or less likely to maintain contact with study staff. In the presence of differential loss to follow up, the data from participants who remain under observation would be biased for related outcomes. Substantial baseline characteristic data on patients should be available to quantitatively evaluate whether there are significant differences between patients lost to follow-up and patients with complete follow-up.

Geographical coverage

The geographical coverage will be limited to the sentinel sites that agree to participate in this study. The identification of viral variants in the IC patients may not be generalisable to all parts of GB.

Duration of follow-up

Concerns about the development of novel viral variants resulting from infections in immunosuppressed patients are based in part on the tendency of these patients to develop prolonged infections. The proposed design may not be able to detect the development of these variants if they develop later in the course of a prolonged infection (>28 days), or if they fail to rise above the threshold of detection for the sequencing assay. The feasibility of linkage with routinely collected samples (as per standard of clinical care) for spike protein monitoring in patients who remain SARS-CoV-2 positive beyond Day 28 will be explored (see Section 8.7.2).

Role of Sotrovimab

Immunosuppressed populations are of particular concern for the development of novel variants because of their tendency to develop prolonged infections, which can expose SARS-CoV-2 to the host's antibodies (or therapeutic antibodies or donor-derived antibodies in normal human immunoglobulin products) without viral clearance and create selective pressure for viral mutations allowing for immune evasion. This patient population is of public health interest for sentinel surveillance in the detection of variants of interest and concern, and the proposed study will contribute valuable information to the effort being undertaken by UKHSA. However, the lack of an untreated comparator group in the proposed study design means that it will not allow for any meaningful inference into the association between treatment with sotrovimab and the development of novel viral mutations. Genomic databases (e.g. GISAID) will be used to contextualise the changes in AA from baseline that are identified in the SARS-CoV-2 spike protein in this study.

8.10. Study Closure/Uninterpretability of Results

Information Bias

Relying on investigators to fill out the assessment forms might induce the presence of missing data, which can result in bias. Entry of prospectively collected data into eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff with appropriate training will minimise the amount of missing data.

Rules about how missing data will be handled will be included in the SAP.

Patients Lost to Follow-up or without Follow-up Data

See Section 8.9

8.11. Other Aspects

Not Applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval and Subject Consent

9.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmacovigilance Practices (GVP) Modules V, VI and VIII.

It is the responsibility of GSK and the Investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IEC/Competent Authorities. Any necessary extensions or renewals of IEC approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
- Notifying the IEC of SAE or other significant safety findings as required by IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines (if applicable), the IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

9.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3. Informed Consent Process

Informed consent will be obtained from all patients before enrolment into the study. Each investigator will ensure that each patient who needs to provide informed consent is given full and adequate oral and written information about the nature and purpose of the study. The patient will be given the opportunity to ask questions and allowed time to consider the information provided. All parties will ensure protection of participant personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations.

The signed and dated informed consent must be obtained before any study procedures including sample collection or data entry into the eCRF. The investigator must store the original, signed ICF. A copy of the signed ICF must be given to the patient. If the patient decides not to participate, the reason will be collected in the eCRF. The option of using e-Consent will be explored and the process by which consent is collected will be updated as needed and provided to sites via other means.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about sotrovimab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have sotrovimab approved for medical use or approved for payment coverage.

9.2. Participant Withdrawal

Participation in this study is voluntary and patients may withdraw from the study at any time without prejudice. If the patient withdraws or is withdrawn, the reason will be collected in the eCRF. The ICF will explain that in case of withdrawal, all study data collected before withdrawal will be kept in the study database.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The process of managing subject samples collected but not analysed at the time of withdrawal will be managed following the process as described in the study reference manual. The Sponsor reserves the right, at any time, to discontinue enrolment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons.

9.3. Subject Confidentiality

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The ICF will incorporate wording that complies with relevant data protection and privacy legislation in the UK. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

Study Use means the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Key Definitions

This study adopts the following ICH definitions:

Adverse event: Any untoward medical occurrence in a patient, or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

- An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an AE), and AEs associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device or combination product.

Adverse Drug Reaction (ADR): A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious adverse event: any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalisation or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly.

Spontaneous events:

- Those AEs observed related to the GSK product under evaluation but exempted from collection, if justified, are reported as spontaneous events.

- Those AEs observed related to any other GSK product (not under evaluation)are reported as spontaneous events.
- If any ADRs are observed related to drug product(s) not related to the Sponsor (GSK), the Investigator should report the ADRs to the appropriate marketing authorisation application of the product(s) or Health Authority per local regulations.

More detailed definitions of AE types are provided in the SMP.

The Investigator or Sponsor must provide a causality assessment regarding the relationship of any AE to the medicinal product.

Further details of the causality assessment can be provided in the protocol or the reader can be referred to the SMP.

11.2. Collection of adverse events/reactions

Adverse events (serious and non-serious) will be collected following the administration of sotrovimab if considered related to sotrovimab. Events should only be collected if they are new or worsening when compared to the patient's usual health status. Safety data will be collected by the study research HCP on site at baseline and by phone at Day 7, 14 and 28 (+/-2 days). Only safety events related to sotrovimab will be collected. The study population is likely to have many comorbidities and AEs may be symptoms of their underlying diseases.

As they are not related to study objectives, spontaneously captured AEs related to other GSK products, or non-GSK products, are not systematically collected, but are reported (see adverse event reporting in Section 11.3 below).

11.3. Reporting of adverse events/reactions

All AEs (serious and non-serious) systematically collected and considered causally related to sotrovimab will be entered into the CRF, as well as pregnancy exposures, and should be reported to the GSK Case Management Group. These will be classified as individual case safety reports (ICSRs). Reporting process and timelines are provided in the SMP.

AEs related to any other GSK product, will be classified as spontaneous reports and reported to the Safety department as such.

HCPs (and any study vendor) can report these spontaneous adverse reactions to GSK via the following web link:

https://www.gsk.com/en-gb/contact-us/report-a-possible-side-effect/

Adverse reactions related to non-GSK product, will also be classified as spontaneous reports. Healthcare professionals (and any study vendor) will be informed of the possibility to report these spontaneous adverse reactions to the marketing authorisation holder of the suspected medicinal product (studied or not) OR to the concerned competent authority via the national spontaneous reporting system.

It is the responsibility of the Sponsor of the product in question rather than the Investigator to report these spontaneous ADRs to the Regulatory Authorities according to applicable regulations.

11.4. Safety collection and reporting study documentation

A Safety Management Plan (SMP) will be developed for the study and will provide detailed information on the study specific pharmacovigilance processes and procedures.

- This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:
- Supplier pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs collection, pregnancy exposures and reporting processes
- Health safety information (HSI) collection processes
- Causality assessment
- HSI Reporting processes
- HSI reporting tools/forms Frequency of data review
- Reviewing and reporting results
- Interim reports
- PVP oversight process
- Provision of final study report

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

GSK and/or a designated party will prepare safety and other summary reports, as required by the appropriate regulatory authority. In addition, these data may be summarised periodically for presentation at professional conferences and sessions, as appropriate. GSK is responsible for presentations and/or publications. For studies that are fully or partially conducted by investigators who are not employees of the GSK group of companies, GSK and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. GSK should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. Results from this study will be submitted for publication in international peer-reviewed journals and will be disseminated appropriately to inform MHRA and other regulatory agencies, public health guidance and risk assessment, as well as to relevant expert clinical groups. Any public reporting will contain aggregate data and will avoid any risk of deductive disclosure.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Contact details of all Investigators participating in the study will be kept in stand-alone documents.