Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Phase 3 randomized, multi-center, open label study to assess the efficacy, safety, and tolerability of monoclonal antibody VIR-7831 (sotrovimab) given intramuscularly versus intravenously for the treatment of mild/moderate coronavirus disease 2019 (COVID-19) in high-risk non-hospitalized patients; *Safety Substudy assessing the safety and tolerability of single ascending dose monoclonal antibody VIR-7831*

Study Number: VIR-7831-5008 (GSK Study 217114)

Compound Number: VIR-7831 (sotrovimab; GSK4182136)

Abbreviated Title: Intravenous single ascending dose VIR-7831 (sotrovimab) for mild/moderate COVID-19

Sponsor Name: This study is sponsored by Vir Biotechnology, Inc.
GlaxoSmithKline is supporting Vir Biotechnology, Inc. in the conduct of this study.

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Version history

SAP Version (Approval Date)	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0 (10-Aug-2022)	Amendment 4 (27-May-2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report(s) for Study VIR-7831-5008 safety substudy. Details of planned safety and efficacy analyses are provided. This Statistical Analysis Plan (SAP) is based on the protocol amendment 4 dated 27-May-2022. Additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
Safety • Describe the safety and tolerability up through Day 8 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Day 8 • Occurrence of serious adverse events (SAEs) through Day 8 • Occurrence of adverse events of special interest (AESIs) through Day 8 • Occurrence of disease-related events (DREs) through Day 8
Secondary	
Safety • Describe the safety and tolerability up through Week 36 of high dose ascending intravenous sotrovimab	• Occurrence of adverse events (AEs) through Week 12 • Occurrence of serious adverse events (SAEs) through Week 36 (end of study) • Occurrence of adverse events of special interest (AESIs) through Week 12 • Occurrence of disease-related events (DREs) through Week 12
Safety Assess the immunogenicity up through Week 24 of high dose ascending intravenous sotrovimab	• Incidence and titers (if applicable) of serum anti-drug antibody (ADA) and neutralizing antibody (if applicable) to sotrovimab through Week 24
Pharmacokinetics • Assess the pharmacokinetics (PK) up to Week 24 of high dose ascending sotrovimab in serum following IV administration	• IV sotrovimab pharmacokinetics (PK) in serum through Week 24

Objectives	Endpoints
Exploratory	
Efficacy • Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Hospitalization > 24 hours for acute management of illness due to any cause OR • Death
Efficacy • Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of mild/moderate COVID-19	Progression of COVID-19 through Day 29 as defined by: • Visit to a hospital emergency room for management of illness OR • Hospitalization for acute management of illness for any duration and for any cause OR • Death
Efficacy • Evaluate the efficacy up through Day 29 of high dose ascending intravenous sotrovimab in preventing the progression of COVID-19 respiratory disease	• Development of severe and/or critical respiratory COVID-19 as manifested by requirement for respiratory support (including oxygen) at Day 8, Day 15, Day 22, and Day 29
Efficacy • Describe the effect of high dose ascending intravenous sotrovimab on the incidence of ICU stay and mechanical ventilation use through Day 29	• Incidence of participants requiring ICU stay or mechanical ventilation through Day 29
Resistant Mutants • Monitor SARS-CoV-2 resistant mutants against sotrovimab through Day 29	• SARS-CoV-2 resistance mutants to sotrovimab at baseline • Emergence of viral resistance mutants to mAb by SARS-CoV-2
Virologic Activity • Evaluate the virologic activity of high dose ascending intravenous sotrovimab in reducing SARS-CoV-2 viral load through Day 29	• Change from baseline in viral load in nasal secretions by qRT-PCR during follow-up period at Day 5, Day 8, Day 11, Day 15, Day 22 and Day 29 • Undetectable SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5,

Objectives	Endpoints
	Day 8, Day 11, Day 15, Day 22 and Day 29 • Proportion of participants with a persistently high SARS-CoV-2 viral load at Day 8 by qRT-PCR

Primary Estimand

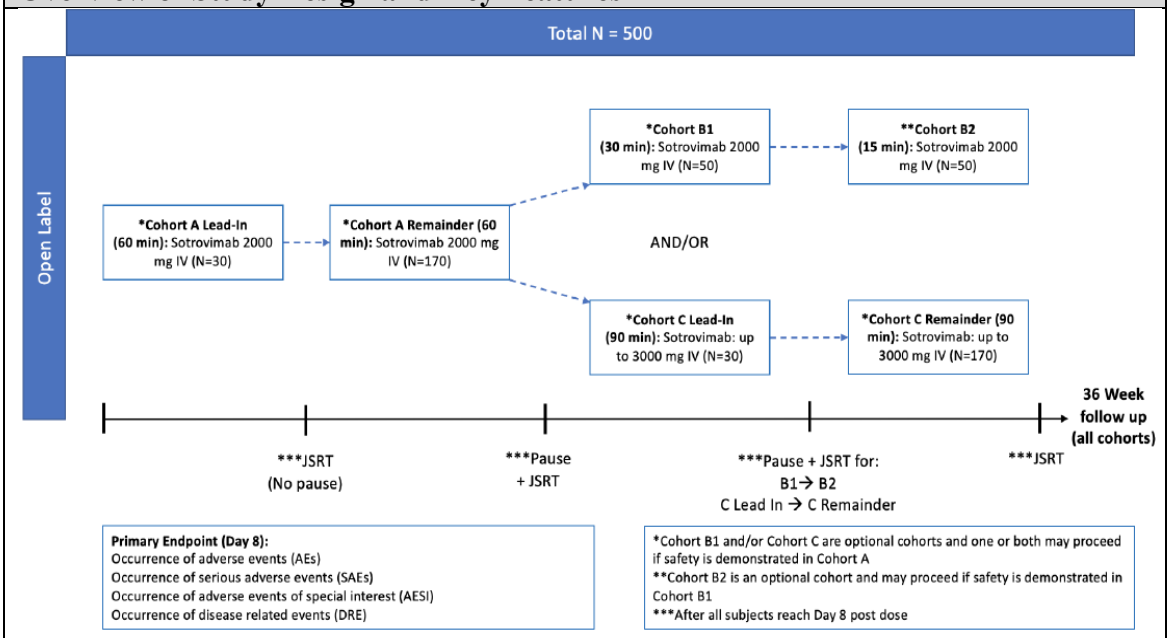
The primary safety endpoint and key secondary safety endpoints will be assessed based on all participants in the Safety analysis set by handling all intercurrent events with a treatment policy strategy (i.e., regardless of the intercurrent events occurring). Data collected in the Safety analysis set will be included in the analysis.

- Population: All participants in the Safety analysis set
- Summary measure: Frequency and percentages
- The anticipated intercurrent events are:
  - Use of medication not permitted during the study as listed in Protocol Section 6.8.1
  - Discontinuation of study intervention as described in Protocol Section 7.1.
  - Death (if not part of the endpoint definition)

All intercurrent events will be handled using a treatment policy strategy where data will be reported as captured.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This substudy is a Phase 3, multi-center, open label, safety study of a single ascending dose level intravenous (IV) sotrovimab, a monoclonal antibody (mAb) against SARS-CoV-2 for the prevention of progression of mild/moderate COVID-19 in participants 18 years old and older at high risk of disease progression. • Approximately 200, and up to 500 participants (with 300 participants designed to be included through optional cohorts) will be enrolled as assigned to an IV infusion of sotrovimab. If multiple cohorts are enrolling at the same time an alternate cohort assignment will be applied. The first cohort, Cohort A, will include approximately 200 participants dosed at 2000 mg IV with a duration of infusion of 60 minutes. Cohorts B1, B2 and C will all be considered optional cohorts for which enrollment can occur following completion of the Cohort A safety assessment by the Joint Safety Review Team (JSRT) [B2 enrollment can occur following JSRT safety assessment of B1]. Cohorts B1 and B2 would each include approximately 50 participants dosed at 2000 mg with durations of infusion of 30 minutes and 15 minutes, respectively. Cohort C would include approximately 200 participants dosed at up to 3000 mg IV with a duration of infusion of 90 minutes (if 3000 mg IV is selected). • Participants with early, mild/moderate COVID-19 who are not on supplementary oxygen and are at risk for disease progression will receive an IV infusion of sotrovimab. • After IV infusion, participants in the safety lead in Cohort A, and potentially Cohort C if a dose higher than 2000 mg is administered,

Overview of Study Design and Key Features	
	will be monitored for 2 hours with vital signs assessments performed at 15 minutes, 30 minutes, 45 minutes, 1 hour and 2 hours. Participants in the remainder of Cohort A (and potentially Cohort C), Cohorts B1 and B2 will be monitored for up to 1 hour. • All participants will be actively monitored on an outpatient basis with frequent collection of safety information through weekly in-clinic evaluations at Weeks 1, 2, 3, and 4, nasopharyngeal swabs for virology and blood draws for PK and ADA sampling as detailed in the Schedule of Activities. • Starting at Week 8, participants will be monitored monthly via phone call or in-clinic evaluation to assess for the incidence and severity of subsequent COVID-19 illness, if any, for a total of 36 weeks from dosing.
Study intervention	• VIR-7831 IV (2000 mg or to a max 3000 mg). • All participants will receive SoC as per institutional protocols, in addition to the study intervention.
Study intervention Assignment	• Participants with early, mild/moderate COVID-19 who are not on supplementary oxygen and at risk for disease progression will be enrolled (should multiple optional cohorts be enrolling at the same time alternate cohort assignment will be applied) to receive an IV infusion of sotrovimab at different doses and durations of infusion. • This is an open label study and all participants enrolled will receive sotrovimab treatment. • Participants will receive sotrovimab IV directly from the investigator or designee, under medical supervision. The date and start and stop times of the dose administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
Interim Analysis	• Analyses at additional weeks during the study may be planned during the course of the study. Analyses after certain number of participants enrolled may be performed based on the review of safety data. • The JSRT comprising individuals from Vir and GSK will review safety and tolerability data from participants in the safety lead in Cohort A and Cohort C, when the enrollment continues. The JSRT will also review each cohort when all participants in a cohort have completed Day 8. • If, during its regular interval review of instream safety data, the JSRT identifies a potential safety concern, the JSRT may escalate this to an ad hoc IDMC meeting for further evaluation.

2. STATISTICAL HYPOTHESES

The primary objective of the substudy is to describe the safety and tolerability of high dose ascending intravenous sotrovimab administered over different doses and durations of infusion. No formal statistical hypothesis testing is planned.

2.1. Multiplicity Adjustment

No formal statistical testing will be conducted in the safety substudy.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility	Study Population
Enrolled	All participants who entered the study Note screening failures (who never passed screening even if rescreened) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Efficacy	All participants who were enrolled and dosed. Participants will be summarized according to the cohort they were assigned to.	Efficacy
Safety	All enrolled participants who were exposed to study intervention. Participants will be summarized according to actual cohort they were in during the study.	Study Population Safety
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be summarized according to the cohort they were assigned to.	PK
Virology	All participants in the Safety analysis set with a lab confirmed quantifiable baseline nasopharyngeal swab at Day 1. Participants will be summarized according to actual dose received	Efficacy (Virology)

Analysis Set	Definition / Criteria	Analyses Evaluated
	during the study. This will be the primary analysis set for virology.	

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Efficacy analysis set will be used for all Efficacy analyses, unless otherwise specified. The Safety analysis set will be used for Study Population summaries and all safety analyses, and for virology analyses of SARS-CoV-2 resistance mutants to sotrovimab. The PK analysis set will be used for all PK analyses. Virology analysis set will be used for Virology analyses related to the evaluation of SARS-CoV-2 viral load.

No formal statistical testing will be conducted. Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), minimum, P25, median, P75, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Efficacy data will be reported according to nominal time of clinical visits unless otherwise stated. Oxygen supplementation and healthcare resource utilization use will be listed. Additional descriptive summaries for oxygen supplementation and healthcare resource utilization may be presented in case there are enough data to summarize.

All data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol unless stated otherwise. It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative and will not, therefore, be provided.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits and the screening visit. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For endpoints assessed using an analysis set other than the Safety analysis set, the baseline value for participants who are enrolled and not dosed will be the latest assessment with nominal visit on or prior to Day 1.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.3. Missing Data Handling Rules

- Missing data can occur due to study withdrawal or participants lost to follow-up before the completion of the study or due to intermittent missing values (i.e., data between two non-missing assessments).

- A treatment policy strategy will be used for all intercurrent events where all data captured will be included in the summary, unless otherwise specified.

The following rule will be applied to viral load endpoints:

- The imputation logic when a sample is reported as 'NEG' (below lower-limit of detection) or '<2.08' (below lower-limit of quantification) is to impute as 0.5 x 120 copies/ml = 60 copies/ml = 1.78 $\log_{10}$ copies/ml

4.2. Primary Endpoint Analyses

4.2.1. Definition of Primary Endpoint

The primary analyses to evaluate the safety and tolerability of high dose ascending intravenous sotrovimab will be performed on the Safety set.

The primary endpoints are:

- Occurrence of adverse events (AEs) through Day 8
- Occurrence of serious adverse events (SAEs) through Day 8
- Occurrence of adverse events of special interest (AESIs) through Day 8
- Occurrence of disease related events (DREs) through Day 8

For each endpoint mentioned above, the primary analysis will include all events with onset date on or after Day 1 of study intervention. These data will also be listed.

4.2.2. Main analytical approach

A Treatment Policy Strategy will be considered for all possible intercurrent events where data will be reported as captured.

The primary endpoint will be summarized using counts and percentages of the number of participants with:

- Any AE
    - All
    - AEs related to study intervention
    - AEs leading to permanent discontinuation of study intervention,
    - AEs leading to temporary interruption of study intervention
- Any Max Grade 3 and 4 AEs
    - All
    - AEs related to study intervention
    - AEs leading to permanent discontinuation of study intervention,
    - AEs leading to temporary interruption of study intervention
- Any SAE
    - All

- SAEs related to study intervention,
- fatal SAEs
- fatal SAEs related to study intervention

Adverse events will be coded using the latest version of the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS 2017 v2.1.

A listing with all AEs, and a listing of AESIs will be provided.

The following adverse events will be considered of special interest (AESI) and will be presented in a listing. Additionally, infusion related reactions (IRR) including hypersensitivity reactions (HSR) within 24 hours of start of infusion will be summarized using frequency and percentages.

- Infusion related reactions (IRR) including hypersensitivity reactions (HSR) within 24 hours of start of infusion. They will be identified using a list of MedDRA preferred terms confirmed by the Safety team.
- Hypersensitivity reactions occurring at any time post dose.
- Local infusion site reactions (ISR) will be identified using a list of MedDRA preferred terms confirmed by the Safety team.
- Immunogenicity (Anti-Drug Antibodies (ADA)) related adverse drug reactions will be reported. These potential events of ADAs will be detected by reviewing AEs that indicate HSR in those participants who have positive anti-drug antibodies. The review will be performed by the Safety team.
- Adverse events potentially related to antibody-dependent enhancement of disease (ADE) will be reported. These potential events of ADEs will be detected by reviewing adverse event/serious adverse events for an increase in the incidence and severity of COVID complications for a participant that cannot be explained by underlying risk factors. The review will be performed by the Safety team.

A listing of disease-related events, that is, events related to expected progression, signs, or symptoms of COVID-19, unless more severe than expected for the participant's current clinical status and medical history or resulting in hospitalization will be provided. These events will be captured on the disease related event CRF.

4.3. Secondary Endpoints Analyses

The secondary endpoints will be based on the Safety analysis set, unless otherwise specified.

4.3.1. Definition of Secondary Endpoints

4.3.1.1. Safety and tolerability

Adverse events analyses including the analysis of adverse events (AEs), serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs through Week 12 (or Week 36 for SAE) will be produced, including counts and percentages of participants with

- Any AE
  - All
  - AEs related to study intervention
  - AEs leading to permanent discontinuation of study intervention,
  - AEs leading to temporary interruption of study intervention
- Any Max Grade 3 and 4 AEs
  - All
  - AEs related to study intervention
  - AEs leading to permanent discontinuation of study intervention,
  - AEs leading to temporary interruption of study intervention
- Any SAE
  - All
  - SAEs related to study intervention,
  - Fatal SAEs
  - Fatal SAEs related to study intervention

Additionally, infusion related reactions (IRR) including hypersensitivity reactions (HSR) within 24 hours of start of infusion will be summarized using frequency and percentages.

Adverse events will be coded using the latest version of the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS 2017 v2.1.

Summary tables below will be presented if at least 5 participants are observed to have any events among all participants, unless otherwise specified.

The count and percentage of AEs (all grades) will be summarized and displayed in descending order by system organ class (SOC) and preferred term (PT). In the SOC row, the number of participants with multiple events under the same SOC will be counted once.

AESIs as outlined in Section 4.2.2 will be summarised using counts and percentages separately.

AEs by maximum severity will be presented. The summary will use the following algorithms for counting the participants:

  - Preferred term row: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

- Any event row: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate listing will also be provided for study intervention-related SAEs.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e., the summary table will include events with the relationship to study intervention as "Yes" or missing.

In addition to the AE overview summary, common AEs defined as any AE preferred term (PT) with an incidence of at least 5% in any of the different doses/durations of infusion will be summarized using counts and percentages separately.

A summary of number and percentage of participants with disease-related events will be provided. In addition, an overview summary of the DREs will be produced. These events will be captured on the disease related event CRF. This data will also be listed.

The following are examples of events NOT meeting the AE definition but will be classed and captured separately as disease progression events in the CRF:

- hypoxemia due to COVID-19 requiring supplemental oxygen
- hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices
- respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO

In addition, a summary of non-serious drug-related AEs and a summary of common non-serious AEs by SOC and preferred term will be provided. A separate summary by SOC and PT of SAEs (number of participants and occurrences) and a separate summary of common (≥5% within a cohort) non-serious AEs (number of participants and occurrences), will also be provided.

4.3.1.2. Immunogenicity of VIR-7831

The incidence and titers (if applicable) of serum ADA to VIR-7831 will be listed and summarized through Week 24 for the Safety analysis set.

Additional immunologic analyses may be conducted and will be documented in a separate technical document.

4.3.1.3. Pharmacokinetics of VIR-7831

Serum pharmacokinetic concentrations will be listed and summarized using descriptive statistics by cohort and visit for the PK analysis set. Any concentration not included in summaries should be flagged in the individual listings with an explanation for the exclusion.

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin.

The non-compartmental analysis will be based on actual sampling times and the parameters will be listed and summarized using descriptive statistics. PK parameters may include, but not be limited to C_{max}, C_{last}, C_{D29}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, AUC_{D1-D29}, $\%AUC_{exp}$, $t_{1/2}$, V_z, V_{ss}, CL.

AUC will be computed using the log down, linear up trapezoidal rule. AUC_{inf} is considered to be well-estimated if $\%AUC_{exp} < 20\%$. In cases where $\%AUC_{exp} > 20\%$, AUC_{inf} and all related parameters (i.e., CL, V_z, and V_{ss}) will be presented in listings but may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist. The decision as to which data points describe the terminal phase will be reached by inspecting the semilogarithmic plot of the data, only considering concentrations at time points beyond T_{max}. A minimum of 3 data points will be used for the estimation of λ_z. For poorly estimated λ_z (i.e., $R^2 \leq 0.80$), the corresponding $t_{1/2}$ values will be excluded from summary statistics. Any parameters for which estimates are available in fewer than 3 participants will be excluded from descriptive statistics. Any parameters not included in summaries should be flagged in the individual listings with an explanation for the exclusion.

Serum concentrations data from this study may be combined with data from other studies evaluating sotrovimab for the purpose of population PK analysis, the details of which will be provided in a separate analysis plan.

4.3.2. Main Analytical Approach

A Treatment Policy Strategy will be considered for all possible intercurrent events where data will be reported as captured, unless otherwise specified.

The secondary safety data of adverse events (including SAEs, AESIs and DREs) will be summarized as described in Section 4.2.2 using counts and percentages.

4.4. Exploratory Endpoints Analyses

The exploratory analyses will be based on the efficacy analysis set, unless otherwise specified.

4.4.1. Definition of Exploratory Endpoints

4.4.1.1. Progression of COVID-19 by Day 29 (hospitalisation for any cause, death)

Progression of COVID-19 through Day 29 as defined by:

- Hospitalization >24 hours for acute management of illness due to any cause
  OR
- Death due to any cause

4.4.1.2. Progression of COVID-19 by Day 29 (emergency room, hospitalisation for any duration or cause, death)

Progression of COVID-19 through Day 29 as defined by:

- Visit to a hospital emergency room for management of illness
  OR
- Hospitalization for acute management of illness for any duration and for any cause
  OR
- Death due to any cause

4.4.1.3. Proportion of Participants Who Progress to Develop Severe or Critical Respiratory COVID-19 through Day 8, 15, 22 and 29

Participants are defined as progressing to develop severe respiratory COVID-19 if they require supplemental oxygen either by nasal cannula, face mask, high-flow oxygen devices, or non-invasive ventilation.

Participants are defined as progression to critical respiratory COVID-19 if they require invasive mechanical ventilation or ECMO.

Participants who die prior to timepoint of interest without first having received supplemental oxygen will be considered to have met the endpoint (composite estimand strategy).

Further detail on the severity of respiratory COVID-19 based on the proportion of participants meeting each tier of the Vir modified version of the NIAID Ordinal Scale for Clinical Improvement (Table 1) will be summarized.

Table 1 Ordinal Scale for Clinical Improvement

Ordinal Scale (Vir modified version, adapted from the Adaptive COVID-19 Treatment Trial [ACTT], 2020; referred to as National Institute of Allergy and Infectious Disease (NIAID) scale hereafter)
1) Not hospitalized, no limitations of activities
2) Not hospitalized, limitation of activities and/or requiring home oxygen [1]
3) Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)
4) Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions)
5) Hospitalized, requiring any supplemental oxygen
6) Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices
7) Hospitalized, receiving invasive mechanical ventilation or ECMO [2]
8) Death

[1] report as category 5 if using oxygen at home (unless were receiving home oxygen pre-morbidly), [2] Participant in receipt of extracorporeal membrane oxygenation (ECMO) at the time of dosing on Day 1 are excluded from the study (participants who subsequently require ECMO may continue in the study).

4.4.1.4. Proportion of participants requiring ICU stay or mechanical ventilation through Day 29

A participant is defined as being on a ventilator if they received invasive mechanical ventilation or ECMO as a form of oxygen therapy. A participant is defined as requiring intensive care if they received an intensive care unit in-patient healthcare encounter of any duration.

4.4.1.5. SARS-CoV-2 Resistant Mutants Against VIR-7831

Summaries and listings of viral resistance mutations at baseline, post-baseline, and treatment-emergent will be provided based on frequency counts in the Safety analysis set.

4.4.1.6. Reduction in SARS-CoV-2 Viral Load

Viral load will be $\log_{10}$-transformed prior to summarizing the data. The Virology analysis set will be used for all analyses, unless otherwise specified.

Reduction of SARS-CoV-2 viral shedding will be summarised by the change from baseline of SARS-CoV-2 nasal viral load at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29.

The proportion of participants with undetectable SARS-CoV-2 in nasal secretions by qRT-PCR at Day 3, Day 5, Day 8, Day 11, Day 15, Day 22, and Day 29 will be summarised. In addition, the proportion of participants with persistently high SARS-COV-2 viral load (PHVL) at Day 8 by qRT-PCR will be summarized using frequency and percentages. PHVL is defined as a viral load value $\geq$4.1 $\log_{10}$ copies/ml at Day 8.

A Kaplan-Meier plot of time to undetectable SARS-CoV-2 in nasal secretions by qRT-PCR by different doses will be produced. For the purposes on the plot, a confirmed negative PCR is defined as first of two or more consecutive negative (no SARS-CoV2 detected) PCR tests.

Summaries of absolute and change from baseline in SARS-CoV-2 viral load (log10 copies/mL) in nasal secretions as measured by qRT-PCR by variants of concern (VOC)/variants of interest (VOI), and by each VOC/VOI will be provided using the Safety analysis set. One listing of VOC/VOI will be provided.

Summaries of absolute and change from baseline in SARS-CoV-2 viral load (log10 copies/mL) in nasal secretions as measured by qRT-PCR by sotrovimab epitope substitution (overall and by each individual epitope amino acid position) will be provided using the Safety analysis set.

A listing of nasal SARS-CoV-2 viral load will be provided using the Safety analysis set where results not included in the summaries of viral load described above are flagged.

4.4.2. Main Analytical Approach

All exploratory endpoints will be summarised only.

The progression of COVID-19 through Day 29 will be summarized using counts and percentages of the number of participants who have progression of COVID-19.

A Treatment Policy Strategy will be considered for all possible intercurrent events where data will be reported as captured, unless otherwise specified.

4.5. Safety Analyses

The safety analyses will be based on the Safety analysis set, unless otherwise specified.

4.5.1. Extent of Exposure

Participants will receive an IV infusion of sotrovimab at different doses and durations of infusion. Depending on which cohort the participant is enrolled in, the intravenous sotrovimab will be administered over different durations of infusion (2000 mg infused over 60 minutes [Cohort A, planned], 30 minutes [Cohort B1, optional] and 15 minutes [Cohort B2, optional]) and up to 3000 mg (infused over 90 minutes [Cohort C, optional]).

The duration of administration will be summarized using counts and percentages over three categories based on target infusion times. For instance, the duration of administration will be categorized as <60 min, =60 min, and >60 min for Cohort A.

Summaries of exposure will be limited to the number of participants exposed and the number of participants with interruptions or infusions stopped early and not completed.

4.5.2. Adverse Events

Adverse events will be summarized as described in Section 4.2 and Section 4.3.

4.5.2.1. Disease-Related Events (not classified as AEs)

Disease-related events as described in Section 4.2.2 will be summarised for each cohort by overall frequency.

4.5.3. Laboratory Data

Summaries by shift tables of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS 2017 v2.1. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 2, any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0.

For laboratory tests with both low and high graded values, summaries will be provided separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

Any clinically abnormal laboratory results which are not identified as AEs will be summarised separately, identification of such values will be described in the OPS document.

For lab tests that are not gradable by DAIDS 2017 v2.1, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

Summaries and listings for hematology, and chemistry laboratory tests will be produced separately. Liver function laboratory tests will be included with chemistry lab tests.

Separate summary of hepatobiliary laboratory events (if any) including possible Hy’s law cases will be provided in addition to what has been described above.

Possible Hy’s law cases are defined as elevated alanine aminotransferase (ALT) > 3×upper limit of normal (ULN), total bilirubin ≥ 2×ULN or international normalized ratio (INR) >1.5. Total bilirubin ≥ 2×ULN can be within 29 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin.

The summary will be produced for worst case post baseline only. A plot for maximum post-baseline Total Bilirubin against ALT will also be produced.

4.5.4. Vital Signs

Summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 1, increase to Grade 2 and increase to Grade 3. The summaries will be produced for worst case post baseline, as well as by post baseline timepoint.

The grade definitions for SBP and DBP are:

Vital Sign Parameter	Units	Clinical Grade Range			
		Grade 0	Grade 1	Grade 2	Grade 3
Systolic Blood Pressure	mmHg	<120	120-139	140-159	>=160
Diastolic Blood Pressure	mmHg	<80	80-89	90-99	>=100

In addition, summaries of respiratory rate, heart rate and temperature will be provided.

A boxplot will be presented for blood pressures by actual cohort. A summary of temperature will also be presented by planned visit/timepoints and pre-defined categories i.e., <38ºC, 38ºC-<38.4ºC, 38.4ºC-<38.9ºC, 38.9ºC-<40ºC and ≥40ºC.

In addition, listings of vital signs parameters (blood pressure, respiratory rate, heart rate and temperature) by visit will be provided.

4.5.5. Oxygen Saturation

Summaries of actual and changes in blood oxygen saturation (SpO_2) will be provided in addition a listing of participants administered oxygen.

Requirement for respiratory support is assessed according to the following categories:

1. Room air
2. Low flow nasal canulae/face mask
3. Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support)
4. Mechanical ventilation /extra-corporeal membrane oxygenation
5. Other
6. Death

Changes in requirement for respiratory support (excluding room air) will be summarized using proportions of participants with change from baseline to higher respiratory support in each category by study day using a stacked bar chart.

4.6. Interim Analyses

The JSRT comprising individuals from Vir and GSK will review safety and tolerability data from each cohort when all participants in a cohort have completed Day 8. If, during its regular interval review of instream safety data, the JSRT identifies a potential safety concern, the JSRT may escalate this to an ad hoc IDMC meeting for further evaluation.

Analyses at additional weeks during the study may be planned during the course of the study. Analyses after certain number of participants enrolled may be performed based on the review of safety data.

4.7. Changes to Protocol Defined Analyses

Recruitment to Cohort A was paused when N=81 and a Day 29 analysis of these participants will be performed.

5. SAMPLE SIZE DETERMINATION

A sample size of approximately 200, and up to 500 participants (with 300 participants designed to be included through optional cohorts as determined by the Joint Safety Review team (JSRT)) was selected to assess the safety profile of an increased dose of sotrovimab robustly and efficiently. The first cohort, Cohort A, will include approximately 200 participants dosed at 2000 mg IV with a duration of infusion of 60 minutes. With 200 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 1.14%. Of note, in COMET-ICE, the infusion related reaction (IRR) rate was 1.14%.

Cohort B1 is optional and can occur after Cohort A if there are no significant safety signals or concerns found in Cohort A. It would include approximately 50 participants dosed at 2000 mg with a duration of infusion of 30 minutes. With 50 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 4.5%.

Cohort B2 is optional and can occur after Cohort B1 if there are no significant safety signals or concerns found in Cohort A or B1. It would include approximately 50 participants dosed at 2000 mg with a duration of infusion of 15 minutes. With 50 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 4.5%.

Cohort C is optional and can occur after Cohort A if there are no significant safety signals or concerns found in Cohort A. It would include approximately 200 participants dosed at up to 3000 mg IV with a duration of infusion of 90 minutes (if 3000 mg IV is selected). With 200 participants, there is a 90% chance of observing at least one particular adverse event of interest, if the true incidence rate of that adverse event is not below 1.14%.

The precision of event rate estimation is shown in the table below, as indicated by the width of 95% confidence intervals. More specifically, the total number of 500 participants reflects the precisions when summarizing over all cohorts, and the total number of 300 participants reflects the precisions when summarizing over all 2000 mg cohorts.

Precision of Estimated Event Rate

Total Number of Participants	Number of Participants with a Particular Event	Event Rate	95% Confidence Interval
500 (overall study size, including Cohorts A, B1, B2, and C)	3	0.5%	(0.12%, 1.74%)
	5	1.0%	(0.33%, 2.32%)
	10	2.0%	(0.96%, 3.65%)
	25	5.0%	(3.26%, 7.29%)
	50	10.0%	(7.51%, 12.97%)
	250	50.0%	(45.53%, 54.47%)
300 (combined number of participants dosed at 2000 mg, includes Cohorts A, B1 and B2)	2	0.5%	(0.08%, 2.39%)
	3	1.0%	(0.21%, 2.89%)
	6	2.0%	(0.74%, 4.30%)
	15	5.0%	(2.83%, 8.11%)
	30	10.0%	(6.85%, 13.97%)
	150	50.0%	(44.20%, 55.80%)
200 (individual study size for Cohorts A or C)	1	0.5%	(0.01%, 2.75%)
	2	1.0%	(0.12%, 3.57%)
	4	2.0%	(0.55%, 5.04%)

Total Number of Participants	Number of Participants with a Particular Event	Event Rate	95% Confidence Interval
	10	5.0%	(2.42%, 9.00%)
	20	10.0%	(6.22%, 15.02%)
	100	50.0%	(42.87%, 57.13%)
50 (individual study size for cohorts B1 or B2)	0	0.5%	(0.00%, 7.11%)
	1	1.0%	(0.05%, 10.65%)
	1	2.0%	(0.05%, 10.65%)
	3	5.0%	(1.25%, 16.55%)
	5	10.0%	(3.33%, 21.81%)
	25	50.0%	(35.53%, 64.47%)

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety Set, unless otherwise specified. Please see Section 3 of the SAP for more information on analysis sets.

6.1.1. Participant Disposition

A summary of subject status and subject disposition for the study conclusion record will be provided. This display will show the number and percentage of subjects who completed the study and who withdrew from the study, including primary and secondary reasons for study withdrawal and presented in the order they are displayed on the collection form. A subject is considered to have completed the study if he/she has completed the Week 36 visit. The end of the study is defined as the date of the last contact of the last subject in the study.

A summary of the number and percentage of subjects who passed screening and entered the study or who failed screening and therefore were not entered into the study, will be

summarized along with the reasons for failure will be summarized for those subjects who failed screening. This summary will be produced based on the Screened analysis set.

The number of subjects will be summarized by Country, Site Id. and Investigator Id. This summary will be produced based on the Enrolled analysis set

A summary of the duration in days in follow-up since infusion/injection will be summarized categorically for the Safety analysis set. The duration is calculated using the following formula:

min (Date of study withdrawal, Date of Data Cut, Date of Study Completion) – Date of Dosing +1

where the earlier date of either a subject withdrawal from the study, the current data cut date, or the date a subject completed the study are used. The summary will display duration overall and by mortality status: alive or deceased. The study withdrawal date for deceased subjects coincides with their death date. Duration categories post-dose include:

- Less than 5 days
- 5 to 10 days
- 11 to 14 days
- 15 to 29 days
- Greater than 29 days
- Greater than 85 days
- Greater than 141 days
- Greater than 169 days
- Greater than 224 days

A summary of treatment exposure will display the number of subjects exposed, the duration of treatment administration, and the number of subjects with infusion/injection interrupted or stopped early and not completed using the Safety set.

A summary of the number of subjects in each of the analysis sets described in the SAP Section 3 will be provided. Also, a listing will display subject exclusions from any analysis set using the Screened analysis set.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age including age categories, race, ethnicity, sex, baseline height, baseline BMI and its categories) will be summarized by descriptive statistics. An additional summary of age ranges using the EMA clinical trial results disclosure requirement categories will be produced and is based on the Enrolled analysis set (see SAP Section 3).

The high-level FDA race categories and detailed race subcategories collected on the CRF will be summarized along with categories for mixed race based on the Intent-to-treat analysis set.

Number of positive SARS-CoV-2 results, specimen type used for SARS-CoV-2 test, diagnostic method, risk factors for COVID-19 progression (as listed in the Protocol Inclusion Criteria), number of COVID-19 conditions met, types of symptoms present, and symptom duration will be summarized.

Additionally, the Baseline Disease Characteristics table will summarize subjects with a baseline obesity risk factor as (BMI ≥30kg/m2) and summarize COPD risk factor to include the following protocol-defined conditions: history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion.

Medical conditions collected at screening will be summarized separately by past and current. These factors will be summarized as collected for current medical conditions at screening.

6.1.3. Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized. Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important.

Data will be reviewed prior to freezing the Day 29 database to ensure all important deviations are captured and categorized in the protocol deviations SDTM dataset.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug coding dictionaries. However, they will only be summarized using the GSK Drug dictionary. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Anatomical Therapeutic Chemical (ATC) Level 1 (Body System) and by Ingredient. Standard of care concomitant medications taken for COVID-19 will also be summarized. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Concomitant Medications will be summarized and listed, while prior medications will be listed.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

This study will not be utilizing lab parameter ranges defining potential clinical important values.

Instead, summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS 2017 v2.1, if available.

6.2.2. Laboratory Values with DAIDS 2017 v 2.1 Grading

Laboratory parameters of interest	Grade			
	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L) > 7 days of age	800 to 1,000 0.800 x 10^9 to 1.000 x 10^9	600 to 799 0.600 x 10^9 to 0.799 x 10^9	400 to 599 0.400 x 10^9 to 0.599 x 10^9	< 400 < 0.400 x 10^9
Absolute Lymphocyte Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 x 10^9 to < 0.650 x 10^9	500 to < 600 0.500 x 10^9 to < 0.600 x 10^9	350 to < 500 0.350 x 10^9 to < 0.500 x 10^9	< 350 < 0.350 x 10^9
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 10^9 to 2.499 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	< 1,000 < 1.000 x 10^9
Hemoglobin16, Low (g/dL; mmol/L) ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34

Laboratory parameters of interest	Grade			
	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
Hemoglobin16, Low (g/dL; mmol/L) ≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 <4.03
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 10^9 to < 125.000 x 10^9	50,000 to < 100,000 50.000 x 10^9 to < 100.000 x 10^9	25,000 to < 50,000 25.000 x 10^9 to < 50.000 x 10^9	< 25,000 <25,000 x10^9
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Potassium, High (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x subject's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x subject's baseline	≥ 3.5 x ULN OR Increase ≥ 2.0 x subject's baseline

Laboratory parameters of interest	Grade			
	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
Creatinine Clearance or eGFR, Low *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from subject's baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR 30 to < 50% decrease from subject's baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from subject's baseline or dialysis needed
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

6.2.3. Study Period

Study phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is prior treatment start, or if end date is missing but the medication end reference equals BEFORE.
Concomitant	Any medication that is not a prior

Study Treatment Emergent Flag for Adverse Event

Flag	Definition
Study Treatment Emergent	If AE onset date is on or after study treatment start date: • Study Treatment Start Date ≤ AE Start Date

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.
- All Adverse Events tables and figures will be presented for Treatment Emergent AEs. AE listings will display all data.

6.2.4. Study Day and Reference Dates

The safety reference date is the study treatment start date and will be used to calculate study day for all safety measures.

For efficacy, measurements of progressions including: all Hospitalizations, Oxygen Supplementation, and Death will measure from treatment start date to align with safety measurements. Efficacy measurements of all-cause mortality and incidence & duration of ICU, Hospitalization, and Ventilation will calculate study day from date of dosed.

- Ref Date = Missing → Study Day = Missing
- Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
- Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

6.2.5. Multiple measurements at One Analysis Time Point

Where duplicate records exist per scheduled visit/time point/participant (if applicable) in vital signs (including oxygen saturation), laboratory data, and ECG measurements the latest record will be used for summaries.

Subjects having both High and Low values for DAIDS 2017 v2.1 or Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance (PCI) summary tables where instead of PCI ranges DAIDS 2017 v2.1 or Normal ranges will be considered for reporting of clinically important safety findings.

All data from scheduled and unscheduled visits will be reported in the listings.

6.2.6. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing. o Answers such as "Not applicable", "Not evaluable" and "Not Done" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Efficacy Endpoints	Details around the missing data handling for efficacy endpoints are described in Section 4.4.2. In addition: • For the exploratory binary endpoint of proportion of subjects who have progression of COVID-19 (i.e., hospitalisation (any duration) OR emergency room visit OR death) through Day 29, missing data will be handled as for the primary endpoint.
Safety Endpoints	• No missing data imputation will be performed for safety endpoints. • Data will be reported as captured.

6.2.7. Handling of Missing and Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in subject listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>

If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.
Else if study treatment start date is not missing:

If month and year of start date = month and year of study treatment start date, then

If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.
Else set start date = study treatment start date.

Else set start date = 1st of month.

</td></tr>
<tr><td>Missing start day and month</td><td>

If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.
Else if study treatment start date is not missing:

If year of start date = year of study treatment start date, then

If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.
Else set start date = study treatment start date.

Else set start date = January 1.

</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications</td><td>

Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:

</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
o If month and year of start date = month and year of study treatment start date, then
▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.
▪ Else set start date = study treatment start date.
• Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
o If year of start date = year of study treatment start date, then
▪ If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.
▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Oxygen Supplementation</td><td>
<table>
<tr><td>Completely missing end date</td><td>If the end date is missing and subsequent record exists and is not missing the start date, impute the missing end date as the start date of the subsequent record.

If end date is missing and no subsequent record exists, the method of oxygen supplementation will be considered ongoing at time of database extraction.</td></tr>
</table>
</td></tr>
<tr><td>Age</td><td>Age will be imputed from year of birth. The calculation will use 30 June as the day and month and will calculate the age relative to Screening date.</td></tr>
</table>

6.2.8. Early PK Access Key Activities

PK dummy activities will be performed as per the standard process. The details of dummy activities will be explained in the OPS.

6.2.9. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
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