Reporting and Analysis Plan

Study ID: 207959

Official Title of Study: A Phase 2a Multicentre, Randomized, Open-Label, Two-Part Adaptive Design Study to Evaluate the Antiviral Effect, Safety and Tolerability of GSK3810109A, an HIV-1 Specific Broadly Neutralizing Human Monoclonal Antibody in Antiretroviral-naïve HIV-1-Infected Adults

NCT Number-NCT04871113

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Title Page

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Study Number: 207959

Compound Number: GSK3810109A

Short Title: Phase 2a (PoC) Multicenter, Randomized, Adaptive, Open-label, Dose-Ranging Study to Evaluate Antiviral Effect, Safety, Tolerability and Pharmacokinetics of GSK3810109 in HIV-1 Infected Adult Subjects
BANNER: **B**roadly-neutralizing **A**ntibody **N**6LS in ART-**N**aives to Evaluate virologic **R**esponse

Sponsor Name: ViiV Healthcare UK Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	11 May 2021	Amendment 3, 11MAR2021	Not Applicable	Original version
SAP Amendment 1	07 Jul 2022	Amendment 4, 26JUL2021	• Add safety population for efficacy analysis of treatment effect based on treatment received. • Add additional analysis of CD4+ percent change from baseline and summarize CD4+ change from baseline to time at achieving viral load nadir. Add CD8+ and CD4/CD8 ratio in addition to CD4+. • Add time to viral load rebound analysis. This, this replaces the rederivation of monotherapy endpoint criteria as well as time on monotherapy analysis. • Remove criteria for PP analysis. Primary analysis will be repeated on the PP analysis set. • Add absolute bioavailability analysis for the 700 mg SC and IV Cohorts chosen for Part 2. • Add dose-proportionality assessment using all IV Cohorts. • Add dose-response and exposure-response modelling based on the IV dosing Cohorts. • Remove impact of COVID assessments and retain a limited subset of COVID analysis focussing on COVID AE's.	Changes followed review of Part 1 data and dose selection for Part 2

			• Add Spearman correlation in place of log transformation for correlation analysis (virology). • Add IC80 to the virology outputs and correlation analysis. Add analysis using normalized values. • Use log10 baseline plasma HIV-1 RNA for correlation analysis. • Replace 'time on monotherapy' with 'time to rebound' and add rules for imputation. • Clarify Section 3.1 number 5 to refer only to monotherapy through Day 11 • Minor clarifying edits throughout	
SAP Amendment 2	30 Jun 2023	Amendment 4, 26JUL2021	• Add EOS analysis summary in 6.1 • Add summary of proportion of responders in 6.1.2 • Add summary of anti-drug antibodies in 6.1.3	EOS reporting

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 207959 following monotherapy completion of Part 1 and Part 2 of the study, once the last participant in Part 2 has completed the monotherapy phase. Details are provided for the planned interim analysis, all primary objectives, and some secondary/exploratory objectives where data is anticipated to be available at the time of analysis.

The second amendment of the SAP provides details in Section 6.1 to describe the analyses to be conducted at the end of study (EoS) completion, including the scope, the update from the primary analysis and rational for the update. The end of the study is defined as the date of the last visit of the last participant in the standard of care follow-up phase of the study or last scheduled procedure shown in the SoA for the last participant in the trial.

Descriptive study population analyses such as summary of demography and baseline characteristics and 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

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the antiviral activity following a single dose of GSK3810109A in treatment-naïve HIV-1 infected participants	Plasma HIV-1 RNA maximum change from Baseline during the monotherapy phase
To assess safety parameters following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Adverse events, Grade 2-4 ALT/ AST, treatment-emergent ECG abnormalities and Grade 2-4 injection site reactions
Secondary	
To characterize the pharmacokinetics of GSK3810109A in treatment-naïve HIV-1 infected participants following a single IV or SC administration	GSK3810109A PK parameters following single dose administration e.g.: AUC (0-t), Cmax, Tmax, Ct
To explore the potency of GSK3810109A	Relationship between GSK3810109A exposure and change in plasma HIV-1 RNA over time.
To assess immunologic changes following a single IV or SC dose of GSK3810109A	Absolute values and change in T cell counts from baseline over time

Objectives	Endpoints
To assess whether anti-drug antibodies develop following a single dose of GSK3810109A	Incidence of and titre in serum of anti GSK3810109A antibodies over time
Safety	
Safety and tolerability of GSK3810109A following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Clinical laboratory parameters, ECGs, vital signs, and injection site reactions over time.
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1.1.2. Estimands

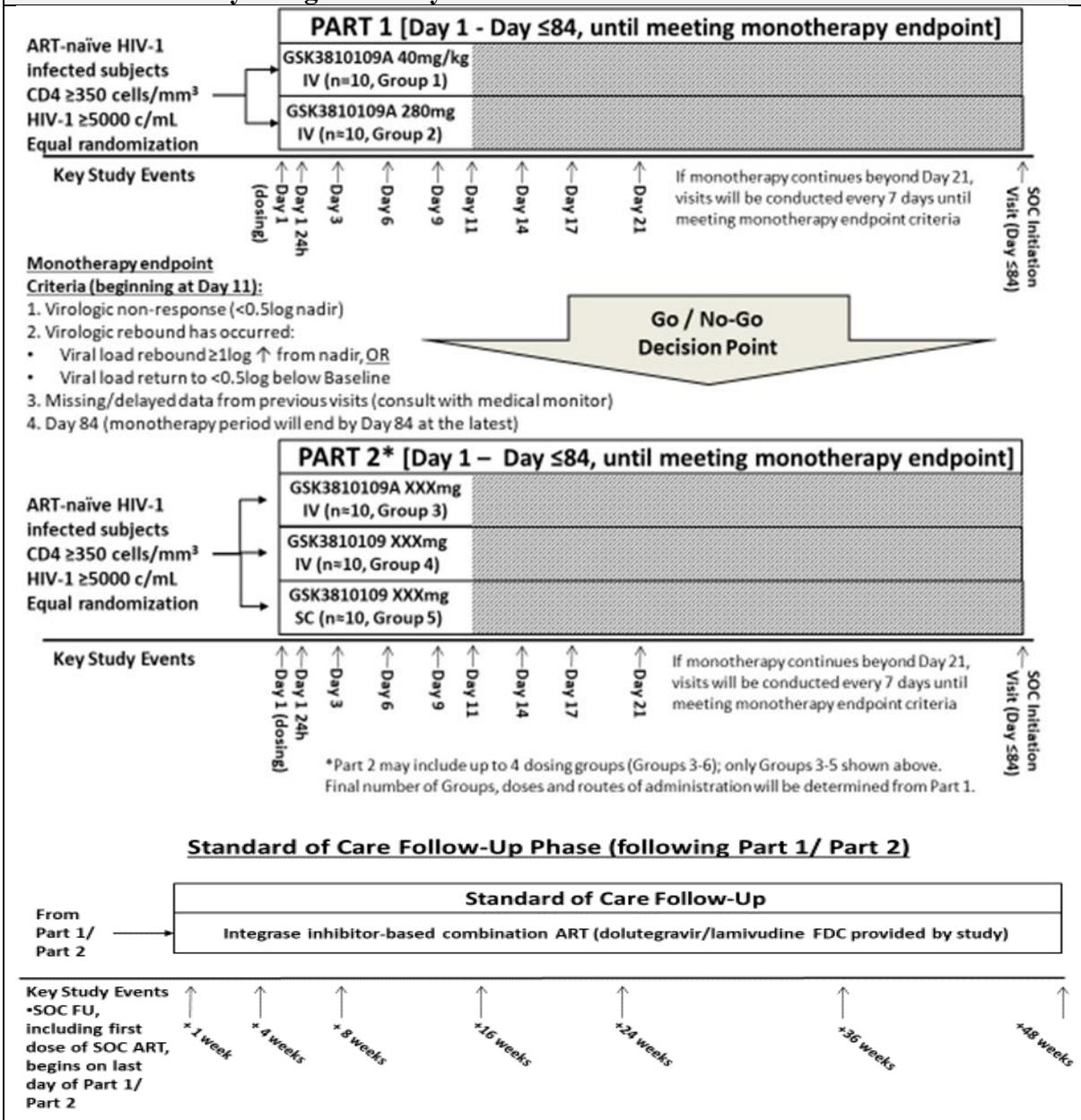
Each study objective is presented below with additional information, including prespecified estimands with related attributes.

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
To evaluate the antiviral activity following a single dose of GSK3810109A in treatment-naïve HIV-1 infected participants	Primary	Plasma HIV-1 RNA maximum change from Baseline during the monotherapy phase	Missing data is handled by the evaluable participant definition which requires plasma HIV-1 RNA measurements at baseline and at least 3 out of the 4 scheduled monotherapy timepoints from Day 3 through Day 11 inclusive. Only evaluable participants will contribute to the estimand. Unevaluable participants are considered missing for the primary estimand (treatment policy).	Mean Log10 maximum change from Baseline during the monotherapy phase
To assess safety parameters following a single dose infusion or SC injection with GSK3810109A in treatment-naïve HIV-1 participants	Primary	Adverse events, Grade 2-4 ALT/ AST, treatment-emergent ECG abnormalities and Grade 2-4 injection site reactions	Treatment policy strategy. All available data will be used. No imputation will be done for missing data due to participant withdrawals.	N (%) for each safety parameter during monotherapy and SOC follow-up.
To characterize the pharmacokinetics of GSK3810109A in treatment-naïve HIV-1 infected participants	Secondary	GSK3810109A PK parameters following single dose administration	Treatment policy strategy. All available data will be used. No imputation will be done for missing data due to missing assessment or participant withdrawals.	Mean and median AUC (0-t), Cmax, Tmax, Ct for each study arm.

Objective	Estimand Category	Estimand Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
following a single IV or SC administration		e.g.: AUC (0-t), Cmax, Tmax, Ct		
To explore the potency of GSK3810109A	Secondary	Relationship between GSK3810109A exposure and change in plasma HIV-1 RNA over time.	Treatment policy strategy. All available data will be used. No imputation will be done for missing data due to missing assessment or participant withdrawals.	Mean and median change from baseline in log10 values over time by each study arm of the monotherapy period.
To assess the immunologic changes following a single IV or SC dose of GSK3810109A	Secondary	T cell counts	Treatment policy strategy. All available data will be used. No imputation will be done for missing data due to missing assessment or participant withdrawals.	Mean and median absolute values and change from baseline for each study arm at each visit.
To assess whether anti-drug antibodies develop following a single dose of GSK3810109A	Secondary	Incidence of and titre in serum of anti GSK3810109A antibodies over time	Treatment policy strategy. All available data will be used. No imputation will be done for missing data due to missing assessment or participant withdrawals.	N (%) for incidence and mean, median for titer values for each study arm at each visit.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• Phase 2a, randomized, open label adaptive design study in HIV-1 infected, treatment-naïve adults. • Participants first enter a screening phase of up to 28 days • Randomized participants will then enter a monotherapy phase (Part 1 or Part 2) of up to 84 days until monotherapy endpoint criteria are reached.

Overview of Study Design and Key Features	
	• All participants will then enter a standard of care follow-up phase of 48 weeks.
Study intervention	Study intervention is a single dose of GSK3810109A administered either intravenously or subcutaneously depending on the study arm.
Study intervention Assignment	Randomized assignment in Part 1 at a 1:1 ratio between 40mg/kg IV dose and 280mg IV dose. Part 2 will be randomized equally at the doses and route of administration chosen at the interim. The following Groups were chosen at the interim and will be randomly assigned for Part 2 at a 1:1:1 ratio: • GSK3810109A Single dose 700 mg IV • GSK3810109A Single dose 70 mg IV • GSK3810109A Single dose 700 mg SC
Interim Analysis	An informal interim analysis will be conducted after enough Part 1 participants complete their monotherapy phase for safety and efficacy analyses (see Protocol Section 9.5).

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested, and study conclusions will be based on estimation. The primary treatment effect to be estimated is the maximum plasma HIV-1 RNA decline from baseline over the Monotherapy Phase for each dose level and method of administration (intravenous or subcutaneous).

No adjustments for multiplicity will be made for any analyses.

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. Participants who were randomised by error are included in the enrolled population. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomized	All participants who were randomly assigned to treatment in the study. This population will be based on the treatment the participant was randomized to.	Study Population
Safety	All participants who received at least one dose of study treatment. This population will be based on the treatment the participant received.	Safety Study Population Efficacy Pharmacodynamic Virology
Full Analysis Set (FAS)	All randomized participants who received at least one dose of study treatment. This population will be based on the treatment the participant was randomized to. Any participant who receives a treatment randomization number will be considered to have been randomized.	Efficacy
Per-Protocol (PP)	All participants in the FAS population who comply with the protocol. Protocol deviations that would exclude participants from the PP population are defined in Section 3.1.	Efficacy The PP set will not be used for analyses if this analysis set comprises more than 90% of the Full Analysis Set (FAS)
Pharmacokinetic (PK)	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ]	PK

Analysis Set	Definition / Criteria	Analyses Evaluated
	values with the actual dose and PK sampling time will be considered as non-missing values).	PK/PD
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Confirmed Virologic Failure (CVF)	• CVF is defined as meeting any of the below: Virologic Non-Response (determined only after SOC Initiation): A decrease in plasma HIV-1 RNA from the SOC Initiation Visit (end of Monotherapy Phase) of less than 2.0 log10 c/mL at SOC Follow-up Week 8, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL, Confirmed plasma HIV-1 RNA ≥200c/mL on or after SOC Follow-up Week 12. Virologic Rebound Criteria: Confirmed rebound in plasma HIV-1 RNA ≥200c/mL after prior confirmed suppression to <200c/mL during SOC Follow-up.	

3.1. Definitions for the Per Protocol Analysis Set

A participant meeting any of the following criteria will be excluded from the Per Protocol analysis set:

Number	Exclusion Description
01	Participant who did not receive correct treatment which the participant was randomized to
02	Participant withdrew from the study before meeting monotherapy endpoint criteria
03	Participant who deviated from any inclusion/exclusion criteria
04	Participant with a probable/suspected/confirmed COVID-19 diagnosis during the first 11 days of monotherapy
05	2 Consecutive monotherapy visits through Day 11 missing or performed out of the window defined in the protocol Table 3.
06	Participant with an Important Protocol Deviation during the study meriting exclusion from the PP analysis set. Protocol deviations will be adjudicated throughout the study and will be classified as important (yes/no), along with the determination if they should trigger exclusion from the PP analysis set.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Safety analysis set will be used for all Study Population, Efficacy, and Safety analyses The FAS will be used for the primary Efficacy analyses. The FAS population will not be used for the remainder of efficacy analysis. This is to group the treatment arms with the treatment actually received, to capture the treatment effects on the objective measure of plasma HIV-1 RNA.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

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. For procedures where there is only a single planned Day 1 assessment scheduled for pre-dose, if time is not collected, the Day 1 assessment can be assumed to be taken prior to first dose and used as baseline.

For purposes of protocol defined virologic failure during the SOC phase, baseline will be the latest assessment prior to SOC initiation. Assessments taken at the SOC initiation visit are assumed to be done prior to SOC initiation as per protocol, unless otherwise noted.

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

4.1.3. Multicenter Studies

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.2. Primary [Endpoint(s)/Estimand(s)] Analyses

4.2.1. Definition of endpoint(s)

The primary endpoint used to construct the primary estimand is plasma HIV-1 RNA (copies/mL) collected at baseline and at each visit during monotherapy. The primary estimand is maximum change from baseline in Log_{10} plasma HIV-1 RNA (c/mL) during the monotherapy phase. Maximum change from baseline is only defined if a participant is evaluable, defined as having plasma HIV-1 RNA measurements at baseline and at least 3 out of the 4 scheduled monotherapy timepoints from Day 3 through Day 11 inclusive.

Maximum change from baseline will be set to missing in the case of insufficient data. Additional participants will be randomized until 10 evaluable participants in the high-dose group is achieved.

4.2.2. Main Analytical Approach

Maximum change from baseline in Log10 plasma HIV-1 RNA (c/mL) during the monotherapy phase will be summarized by treatment group. In addition, maximum change in actual (not log-transformed) plasma HIV-1 RNA from baseline among evaluable participants will be summarized by treatment group.

4.2.3. Sensitivity analyses

The primary analysis will be repeated on the PP population as a sensitivity analysis.

Additionally, if 10% or more participants in the FAS are non-evaluable, the primary analysis will be repeated on the entire FAS population with the following change. The maximum viral load decline will be defined in all participants with a baseline plasma HIV-RNA (copies/mL) measure and at least one post-baseline measure at their day 3 visit or later in monotherapy. This sensitivity analysis will determine whether the maximum decline estimate varies based on the amount of post-baseline timepoints available.

4.2.4. Supplementary analyses

Plasma HIV-1 RNA values and change from baseline (on original scale and log10 scale) will be summarized by treatment group at each visit. This data will also be listed by treatment group, participant, and time point. Mean and median change from baseline (log10 scale) will be plotted by treatment group over the monotherapy phase.

Time to reaching plasma HIV-1 RNA nadir in the monotherapy phase will be summarized by treatment group. Time to rebound (from Day 1) among responders will also be summarized by treatment. Rebound is defined as an increase in plasma HIV-1 RNA of $\geq$1 log10 from nadir or a return to within 0.5 log10 from baseline.

Proportion of participants with plasma HIV-1 RNA decreases from baseline of $\geq$ 0.5 log10, $\geq$1 log10 , $\geq$1.3 log10 and $\geq$1.4 log10 copies/mL during the monotherapy phase will be summarized by treatment group.

Reason for SOC initiation (as detailed in protocol Section 4.2) will be summarized by treatment group.

A mixed-effects linear model will be fitted using plasma HIV-1 RNA change from baseline (on log10 scale) as the outcome measure with baseline plasma HIV-1 RNA (on continuous log10 scale) and all treatment group*visit combinations as fixed (categorical) effects and subject as a random effect. An unstructured covariance matrix will be used, but others may be considered if the model fails to converge. Estimates of the change from baseline for each visit*treatment group combination along with 90% confidence intervals will be presented.

4.3. Secondary [Endpoint(s)/Estimand(s)] Analyses

4.3.1. Pharmacokinetics

The observed systemic GSK3810109A concentrations will be summarized utilizing a non-compartmental analysis across the different dose levels and route of administration. Relevant pharmacokinetic (PK) parameters such as area under the concentration time curve (AUC), peak drug concentration (Cmax), time to maximum concentration (Tmax) will be estimated as data permit. The AUC parameter for each subject may be estimated across different intervals including an interval post dose until the subject starts the standard of care. AUC may also be calculated for the shortest time interval common to all subjects before standard of care has started in any subject.

Emerging preliminary PK data from the study may be analysed to select appropriate doses for Part 2 of the study. Any deviation from the planned analysis will be adequately described in the study report. A model-based population pharmacokinetic (POP PK) analysis may be undertaken using appropriate methodology to characterize the GSK3810109A concentration time profiles. Systemic concentration time data from other clinical study (e.g. First in Human Study) may be combined for the analysis. Similarly, the viral load data may be included in the analyses to develop a population pharmacokinetic-pharmacodynamic (POP PKPD) analysis to characterize the exposure-response relationship between GSK3810109A concentrations and viral load decline. Impact of intrinsic and extrinsic factors (e.g. subject demographics, treatment, disease status) on drug exposure and/or response may be assessed in such analyses. These POP PK and/or POP PKPD analyses will be considered separate from the PK/PD modelling described in this SAP and will be reported separately from the clinical study report. Although unlikely, such population analysis may be undertaken with preliminary emerging data from the study to aid dose selection for subsequent cohorts in Part 2 of the study. Any PK analyses undertaken to aid dose selection for Part 2 will be summarized in the study report.

4.3.1.1. Definition of endpoint(s)

Parameter	Parameter Description
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.
t_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to time t will be calculated using the linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid.
C_t	Concentration at time t

4.3.1.2. Main analytical approach

Derived PK endpoints will be summarised by treatment group using descriptive statistics, graphically presented (where appropriate) and listed.

4.3.1.3. Supplementary analyses

Absolute bioavailability of SC compared with IVSC administration will be estimated using the data from the 2 700mg arms of the study (1 SC and 1 IV). C_{max}, and AUC(0-∞) if available will be analyzed after log_e transformation. Exponentially back-transformed point estimates (absolute Bioavailability of GSK3810109A) and associated 90% confidence intervals for the ratio SC/IV dose will be reported.

Dose proportionality will be estimated from the IV arms of the study. C_{max}, and AUC(0-∞) if available will be analyzed after log_e transformation. The following power model will be useduse:

$$y = \alpha * dose^{\beta}$$

where y denotes the PK parameter (C_{max} or AUC(0-∞)) being analyzed and dose denotes the total dose administered to a subject.

Log_e transformed data will be analyzed by fitting the following linear model:

$$log_e y = log_e \alpha + \beta \, log_e dose$$

Estimates of slope β will be reported along with corresponding 90% confidence intervals. If the CI contains 1 then we shall assume Dose Proportionality to hold.

4.3.2. Immunology

CD4+, CD8+ T-cell count, and CD4+/CD8+ ratio at each assessment visit along with absolute change from baseline and percent change from baseline will be summarized by treatment. Maximum CD4+, CD8+ T-cell count, and CD4+/CD8+ ratio change over the monotherapy phase (absolute and percent) will also be summarized by treatment.

Additionally, CD4+, CD8+ T-cell count, and CD4+/CD8+ ratio change and percent change from baseline to viral load nadir visit will be summarized by treatment. Viral load nadir visit is defined as the visit in which the subject reached the maximum HIV-1 RNA reduction from baseline during monotherapy.

4.3.3. Pharmacodynamic Analyses

4.3.3.1. Definition of Endpoint(s)

The endpoint for this analysis is Log10 plasma HIV-1 RNA Maximum change from baseline over the monotherapy phase.

4.3.3.2. Main Analytic Approach

The relationship between dose and Log10 plasma HIV-1 RNA Maximum change from baseline will explored with an Emax model. Only data from participants in the IV dosing group will be used. The model used will be a simplified Emax model as follows:

$$\Delta VL = \frac{(Emax)}{1 + \left(\frac{ED50}{Dose}\right)} + \epsilon$$

Where:

- ΔVL is the Log10 plasma HIV-1 RNA maximum change from baseline over the monotherapy phase.
- Emax is maximum response
- ED50 is the dose (in mg) that attains the 50% of the maximal effect
- ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The derived data from this Emax model (estimates Emax, ED50 and Variance along with their standard error, and 95% CI) will be tabulated and an dose-response curve will also be produced.

4.3.3.3. Supplementary Analysis

The analysis will be repeated for the following additional endpoints, as data allows:

- Time to monotherapy viral load nadir.
- Time to viral load rebound.

Only responders will be included in the supplemental analysis.

In case the primary Emax model fails to converge or produce reliable estimates, a simpler linear model of the form $\Delta VL = \alpha * PK + \epsilon$ will be used.

4.3.4. Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

4.3.4.1. Definition of Endpoint(s)

The endpoint for this analysis is Log10 plasma HIV-1 RNA Maximum change from baseline over the monotherapy phase relative to Cmax.

4.3.4.2. Main Analytic Approach

The relationship between Cmax and Log10 plasma HIV-1 RNA Maximum change from baseline will explored with an Emax model. Only data from participants in the IV dosing group will be used. The model used will be a simplified Emax model as follows:

$$\Delta VL = \frac{(Emax)}{1 + \left(\frac{EC50}{Cmax}\right)} + \epsilon$$

Where:

- ΔVL is the Log10 plasma HIV-1 RNA maximum change from baseline over the monotherapy phase.
- Emax is maximum response
- EC50 is the Cmax exposure that attains the 50% of the maximal effect
- ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The derived data from this Emax model (estimates Emax, EC50 and Variance along with their standard error, and 95% CI) will be tabulated and an exposure-response curve will also be produced.

4.3.4.3. Supplementary analyses

The analysis will be repeated for the following additional endpoints:

- Time to monotherapy viral load nadir.
- Time to viral load rebound.

Only responders will be included in the supplemental analysis.

In case the primary Emax model fails to converge or produce reliable estimates, a simpler linear model of the form $\Delta VL = \alpha * PK + \epsilon$ will be used.

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4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

Extent of exposure (both in actual dose (mg) and weight-adjusted dose (mg/kg) will be summarized by treatment group. In addition, exposure will be listed (mg and mg/kg) for all participants. For any subcutaneous treatment arm, number of injections will also be summarized.

4.5.2. Adverse Events

AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) using the latest version at time of database release. AEs will be graded by the investigator according to the Division of AIDS (DAIDS) Criteria Version 2.1.

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays will be provided in the Output and Programming Specifications (OPS). The AE analysis will be summarized by treatment group. Summaries will be produced using all Part 1/Part 2/ SOC follow-up data available at the time of analysis. Summaries by study phase (monotherapy or SOC follow-up) will be produced in addition to overall summaries.

The following summaries will be provided:

- Adverse events overview
- All adverse events by SOC and PT and all adverse events by maximum grade and SOC and PT
- Drug related adverse events by SOC and PT and drug related adverse events by maximum grade and SOC and PT
- Serious Adverse Events by SOC and PT (Number of Participants and Occurrences)
- Adverse events leading to withdrawal from study/permanent discontinuation of study treatment
- Common (>= 5%) adverse events by overall frequency
- Common (>= 5%) non-serious adverse events (Number of Subjects and Occurrences)

The following listings will be provided:

- All adverse events
- Subject numbers for individual AEs
- Serious adverse events
- Drug related adverse events
- Adverse events leading to withdrawal from study/permanent discontinuation of study treatment
- Fatal serious adverse events

- Non-fatal serious adverse events

4.5.2.1. Adverse Events of Special Interest

AEs of special interest for this study include: injection site reactions, infusion related reactions,

serious/severe immune reactions (including anaphylaxis and cytokine release syndrome). These AE's will be defined using the applicable MedDRA terms which will be specified in the OPS.

Injection/Infusion site reactions will be summarized by treatment, PT, time to onset and duration. Separate summaries will be produced where each event is counted (event level) and by subject (combining PT events and categorizing grade by worst-case). A listing will also be provided accordingly.

Serious/severe immune reactions, if present, will be presented as a separate summary by treatment group and PT.

4.5.2.2. Impact of COVID-19 Pandemic on Adverse Event Reporting

The incidence of AEs and SAEs (Fatal and Non-Fatal) of COVID-19, COVID-19 AEs leading to study withdrawal, and COVID-19 AEs by severity, will be obtained from standard AE and SAE summaries. COVID-19 assessments and COVID-19 symptoms will be summarized for participants with COVID-19 AE's. Additional descriptive summaries related to COVID-19 may be included in the OPS.

4.5.3. Additional Safety Assessments (if applicable)

4.5.3.1. Laboratory Data

Laboratory values and change from baseline for haematology, clinical chemistry, and liver function parameters will be summarized by visit and by treatment group. Laboratory values for haematology, clinical chemistry, liver function, and urinalysis will also be listed by subject.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) Criteria Version 2.1. Summaries of worst case grade increase from baseline grade will be provided for all the gradable lab tests. These summaries will display, by treatment group, the number and percentage of subjects 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 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. Summaries of worst-case during the monotherapy phase will be produced in addition to overall summaries.

4.5.3.2. ECG

ECG is collected in triplicates at scheduled visits. Average values will be reported in summary tables and triplicate readings will be listed in listings. A summary of the number and percentage of participants with ECG findings will be displayed by treatment

group. For abnormal ECG findings, worst-case will be used in the summaries and all will be included in the listing. Additionally, summary statistics of change from baseline in ECG values will be presented. Maximum QTc values and maximum increase in QTc values post-baseline relative to baseline will be summarized by treatment. All ECG Values for Participants with a Value of Potential Clinical Importance will be listed (potential clinical importance criteria will be specified the OPS). Summaries of worst-case during the monotherapy phase will be produced in addition to overall summaries.

4.5.3.3. Vitals

Vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation (SpO2), temperature, height, weight, and BMI) values and change from baseline at every assessed time point will be summarized (n, mean, standard deviation, median, minimum, and maximum). Height and weight summaries will be included only for screening and Day 1 visits, as per the protocol-defined collection.

The number of subjects with worst case vital sign results relative to normal range criteria which are post-baseline relative to baseline will be summarized by test and category. A by-subject listing of vital signs for all participants with potential clinical importance will be produced. Potential clinical importance criteria will be specified in the OPS. Summaries of worst-case during the monotherapy phase will be produced in addition to overall summaries.

4.6. Other Analyses

4.6.1. Subgroup analyses

Analyses of the primary efficacy endpoint (plasma HIV-1 RNA maximum decline and decline at each study visit) will be repeated by subgroup for:

1. Participants with plasma HIV-1 RNA decline during monotherapy of <0.5 $\log_{10}$ copies/mL and ≥ 0.5 $\log_{10}$ copies/mL.

2. Participants with plasma HIV-1 RNA at baseline of $\leq$ 100,000 copies/mL and >100,000 copies/mL.

5. SAMPLE SIZE DETERMINATION

An estimated 50 participants will be randomly assigned to GSK3810109A across approximately 5 groups to achieve approximately 10 evaluable participants for each group.

The sample size of 10 evaluable participants for Group 1 was chosen to allow for an accurate estimate of the primary treatment effect of the highest dose. A sample size of approximately 10 for the remaining groups was chosen primarily based on feasibility in order to explore approximately 4 additional groups at varying dose concentrations and modes of delivery (IV and subcutaneous). The required sample size of 10 for Group 1 is to be able to account for the possibility of some participants being non-sensitive to

GSK3810109A, and to accurately estimate the primary treatment effect among the sensitive-only subgroup.

Based on viral load decline data from 3 previous POC studies with bNAbs (VRC01: [Lynch, 2015]; 10-1074: [Caskey, 2017]; 3BNC117: [Caskey, 2015]), we assumed a target value viral load decline (VLD) for individual participants from the highest dose (Group 1) to be 1.3 $\log_{10}$ when analysing all participants regardless of their sensitivity to GSK3810109A. We also assumed a minimum value of 1 $\log_{10}$ VLD to represent a clinically meaningful change. Alternatively, a target value of 1.4 $\log_{10}$ VLD among participants sensitive to GSK3810109A represents a meaningful decline to proceed with the study. In the absence of sensitivity data during the study we use a $\geq$0.5 $\log_{10}$ decrease as a proxy for sensitivity for our interim analysis. We used these thresholds in our interim Go/No Go criteria, detailed in Protocol Section 9.5 and powered the study to make a decision on whether to proceed to Part 2 based on the VLD observed in Part 1 among the high-dose group (Group 1).

To determine the operating characteristics of the interim decision and inform our sample size, we simulated trial data as arising from a mixture of 2 normal distributions to describe the VLD among a population consisting of both sensitive and non-sensitive individuals. The mixing parameter is the proportion of non-sensitive individuals in the population and the mean VLD varying for sensitive individuals and 0.2 log10 for non-sensitive individuals, both with SD=0.4. We simulated data with mixing parameters of 0.10 or 0.30 and mean VLD for sensitive individuals ranging from 0.2 log10 to 2 log10 as listed in Table 1.

We simulated 10,000 trials for each unique combination of the above parameter values. For each unique scenario, we calculated the proportion of trials with Go, No-Go, and Consider for the informal interim analysis described in Protocol Section 9.5. These proportions estimate the probabilities of each decision and are shown below in Table 1.

Table 1 Probability Decision at Interim Based on a Sample Size of 10

% non-sensitive participants in population	True Mean log10 c/mL VLD for sensitive participants in population	Probability of Decision at Interim		
		Go	No-Go	Consider
	0.2: No treatment effect	0.0%	99.8%	0.2%
10%	1.1	24.1%	61.7%	14.2%
	1.25	58.0%	26.3%	15.7%
	1.4	83.0%	7.5%	9.5%
	2	96.3%	0.0%	3.7%
30%	1.1	5.4%	87.4%	7.2%
	1.25	19.0%	64.4%	16.7%
	1.4	35.1%	37.3%	27.6%
	2	57.5%	0.6%	41.9%

To assess the sensitivity of the above analysis to the sample size and parameter assumptions we assessed the operating characteristics under the following 4 scenarios:

1. There is no effect on VLD (mean VLD=0 for entire population).

2. GSK3810109A has mean VLD of 1.4 log10 c/mL among sensitive population, but 50% of the population is non-sensitive to GSK3810109A.

3. GSK3810109A has mean VLD of 1.4 log10 c/mL among sensitive population and only 10% of the population is non-sensitive to GSK3810109A.

4. GSK3810109A has mean VLD of 1.4 log10 c/mL among the entire population (i.e. entire population is sensitive to GSK3810109A).

For each scenario we calculated the operating characteristics above for sample sizes of 8, 10, 20, and 50 to see how sensitive the operating characteristics are to sample size. The results are shown in Table 2.

Table 2 Sensitivity to Sample Size and Parameter Assumptions

Scenario	N	Prob. Go	Prob. No Go	Prob. Consider
Treatment doesn't work VLD=0 for all	8	0.0%	99.8%	0.2%
	10	0.0%	99.8%	0.2%
	20	0.0%	99.9%	0.1%
	50	0.0%	100.0%	0.0%
Treatment works well for sensitive participants and 50% non-sensitive (sensitive VLD=1.4 and non-sensitive VLD=0.2)	8	9.3%	58.3%	32.4%
	10	7.1%	65.8%	27.1%
	20	2.6%	79.8%	17.7%
	50	0.0%	91.1%	8.9%
Treatment works well for sensitive participants and 10% non-sensitive (sensitive VLD=1.4 and non-sensitive VLD=0.2)	8	80.7%	6.5%	12.8%
	10	83.0%	7.5%	9.5%
	20	89.4%	4.1%	6.5%
	50	87.1%	0.2%	12.8%
Treatment works well and all participants sensitive (sensitive VLD=1.4)	8	97.6%	0.7%	1.7%
	10	97.9%	0.4%	1.7%
	20	99.2%	0.0%	0.9%
	50	99.9%	0.0%	0.1%

The false positive rates (Prob. Go in scenarios 1 and 2) and false negative rates (scenarios 3 and 4 Prob. No Go) are well controlled <10% across all sample sizes tested. Additionally, an increase in sample size under scenario 3 does not drastically improve power (Prob. Go). Therefore, a sample size of 10 for Group 1 is sufficient for this analysis.

5.1.1. Other variables and/or parameters

5.1.1.1. Clinical Virology

If virology data is available by Database Freeze (DBF), viral genotypic and phenotypic data will be listed by treatment group, subject, and assessment day. Additional listings will present CVFs occurring at any point in the SOC follow-up.

If complete monotherapy phenotypic data for Part 1 cohorts are available by DBF, IC50, IC80 IC90 values at baseline and SOC initiation will be summarized by treatment. Fold change in IC50 and IC90 from SOC to baseline will also be summarized by treatment. The summaries will contain both the actual IC50, IC80, and IC90 values as well as the IC50 and IC90 fold change compared with the reference virus. The IC50, IC80 and IC90 fold change from SOC to baseline will also be summarized with the reference virus adjustment and be presented as fold change ratio. In the event that the reference virus value at SOC and baseline are the same, the fold-change ratio is equivalent to the actual fold change (as the reference values in the numerator and denominator will cancel each other out).

Pearson and Spearman correlations between the following variables will be summarized by treatment group:

- Baseline sensitivity (IC50, IC80 and IC90; $\log_e$-transformed IC50, IC80 and IC90) and time to rebound.
    - For non-responders, Day 11 will be imputed as time to rebound.
    - For responders after Day 11, time to SOC initiation will be used if rebound criteria were not met by the time of SOC initiation.
- Baseline sensitivity (IC50, IC80 and IC90; $\log_e$-transformed IC50, IC80 and IC90) and maximum viral load decline during monotherapy.
- Baseline plasma HIV-1 RNA log10 c/mL and time to rebound.
    - For non-responders, Day 11 will be imputed as time to rebound.
    - For responders after Day 11, time to SOC initiation will be used if rebound criteria were not met by the time of SOC initiation.
- Baseline plasma HIV-1 RNA log10 c/mL and maximum viral load decline during monotherapy.

These correlations will be summarized using both actual IC50 and IC90 values and the reference virus adjusted values using the IC50, IC80 and IC90 fold change (from reference virus) values. Phenotypic sensitivity at baseline by drug and drug class on all participants will be summarized by treatment. Additional descriptive summaries may be provided in the OPS.

5.1.1.2. Patient Reported Outcomes

The Acceptability of Treatment questionnaire is a modified version of the 25-item Chronic Treatment Acceptance Questionnaire: ACCEPT© [Arnould, 2013; Marant, 2009]. This modified version will include approximately 5-6 questions to assess the participant's opinion regarding the medication's administration method, length of treatment, and general advantages/disadvantages. In this modified version, participants will be asked to complete the following 6 questions regarding their acceptance of the treatment attributes: question #2 – administration method convenience; #5 – length of treatment; #14 – medication frequency; #23-25 general medication

advantages/disadvantages. These data will be summarized by treatment and listed by participant.

Participants will complete a diary card following GSK3810109A infusion/injection. This allows participants to record and score the severity of any reactions, record the impact of the infusion/injection on normal daily activities as well as any action taken such as use of analgesic medication following the infusion/ injection. These data will be summarized by treatment group and listed by subject as collected via the diary cards and entered into the CRF.

5.2. Interim Analyses

An informal interim analysis of preliminary antiviral activity will occur after the earlier of the Day 21 visit or end of monotherapy of the last high-dose (Group 1) participant. Antiviral activity will be measured by maximum viral load decline (VLD) from baseline during monotherapy (Part 1) in evaluable participants in the high dose group (Group 1). This analysis will decide Go/No Go based on emerging evidence of efficacy. The Safety and Dose Evaluation Committee (SDEC) will also consider emerging safety data and any available PK data from both dosing groups before deciding whether to proceed with Part 2 of the trial.

The subgroup for the efficacy Go/No Go decision as well as the criteria used will depend on the proportion of evaluable participants who are non-responders, defined as those participants with a maximum VLD less than 0.5 $\log_{10}$. If less than 30% of evaluable participants are non-responders, then the analysis will be based on all evaluable participants in Group 1 (Scenario 1) from the FAS population. If 30% or more of participants are non-responders, then the analysis will include only those participants in Group 1 from the FAS population with a VLD of at least 0.5 $\log_{10}$ (Scenario 2).

For this analysis, the Bayesian posterior probabilities of the mean maximum $\log_{10}$ VLD (based on the Group 1 data used in each scenario) exceeding/not exceeding certain thresholds will be calculated. For the Bayesian calculation, we assume the maximum VLD follows a normal distribution (mean, standard deviation) and the assumed priors are taken to be non-informative, with Normal (0, 100) for mean and Inverse Gamma (0.01, 0.01) for standard deviation. The following decision criteria will be used:

Scenario 1 (< 30% of evaluable participants are non-responders):

If Prob. (maximum $\log_{10}$ VLD >1) ≥70% AND Prob. (maximum $\log_{10}$ VLD>1.3)≥ 10%, the trial will proceed (GO).

If Prob. (maximum $\log_{10}$ VLD>1) <70% AND Prob. (maximum $\log_{10}$ VLD>1.3) <10%, the trial will not proceed (STOP).

Otherwise, the study team will consider the whole preliminary clinical data (e.g. safety, tolerability and PK, as available) and decide whether to proceed (CONSIDER).

Scenario 2 (>=30% of evaluable participants are non-responders):

If Prob. (maximum $\log_{10}$ VLD <1.4) >50%, the trial will not proceed (STOP).

Otherwise, the study team will consider the whole preliminary clinical data and decide whether to proceed (CONSIDER). In this scenario the team will also determine whether to include a pre-screen for GSK3810109A sensitivity if the decision is to proceed with the trial.

If the decision based on Group 1 data is to proceed with the trial, then the antiviral activity of both Group 1 and Group 2 will be reviewed to aid dose selection and mode of administration of monotherapy for the subsequent groups in Part 2.

At the Part 1 interim analysis stage, safety Go / No-Go criteria from the Safety Population are pre-defined as:

No Go:

- If ≥35% of treated participants in Part 1 receiving GSK3810109A have a clinically significant Grade 3 or higher AE trend or laboratory abnormality trend (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride) determined by the SDEC

Go:

- The above safety 'no go' criteria is not met.

The safety interim analysis will be based on all available safety data from the monotherapy phase of Part 1 participants at the time of the interim efficacy data cut-off. >65% of Part 1 participants must complete monotherapy without a clinically significant Grade 3 or lab abnormality trend before the study can proceed with Part 2 (Go decision). Additional ongoing safety data from Part 1 participants until their monotherapy completion will be added to the interim safety analysis until a definitive decision (Go or No Go) can be reached.

5.3. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 3 (Dated: 11-MAR-2021).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 End of Study Analysis

This appendix provides the details of the planned analyses for Study 207959 EOS reporting. The list of data displays can be found in the OPS.

The primary analyses following monotherapy completion of Part 1 and Part 2 of the study was completed based on the SAP amendment 1. This appendix is written to cover only analyses included in the final end of study reporting. All derivations described in the previous version of SAP will be re-used for end of study reporting and only those definitions and derivations that have changed since the primary analysis are described below. This additional appendix summarizes only the key endpoints of interest for the EOS analysis and explains any deviations from the primary analysis. The summary of the EOS analysis plan are described below:

1. No subgroup analysis, hypotheses testing, PD analyses or PK/PD analyses will be performed on data accumulated between primary analysis and EOS.

CCI [redacted]

3. Safety, virology, and Patient Reported Outcomes analysis have been covered in primary analysis and will be updated with available data that has accumulated through EOS.

6.1.1. Study Population

The study population summaries and data listings will be based on the Safety population, unless otherwise specified. The study population outputs will be similar as in the primary analysis with updated data.

6.1.2. Efficacy Analysis

The efficacy summaries and data listings will be based on the Safety population, unless otherwise specified. Overview of the key planned efficacy endpoints:

- Summary of Plasma HIV-1 RNA
  - This will include data through end of study.
- Summary of Change from Baseline in Plasma HIV-1 RNA- Monotherapy Phase- Safety population
  - This primary analysis will be repeated at EOS for completeness but is not expected to change from primary analysis.
- Summary of Proportion of Subjects with Maximum Plasma HIV-1 RNA decline above Threshold (>= 0.5, 1, 1.3, 1.4) by Treatment - Monotherapy Phase
  - This summary will include small n to allow identification of number of subjects will missing data.
- Summary of Monotherapy Endpoint Met
  - This summary will be included at EOS as some monotherapy endpoint were updated in the datasets after primary analysis.

- Summary of Proportion of Responders (Maximum Plasma HIV-1 RNA Decline at least 0.5 log10) by Treatment - Monotherapy Phase
    - This summary is added at EOS to be a dedicated output of number of responders and also to identify number of subjects with missing data (by including small n).
- Summary of CD4+, CD8+ and CD4/CD8 ratio by Visit
    - This summary is added at EOS to summarize actual values in addition to change from baseline, as described in the protocol and previous SAP version. It will also be updated with accumulated data through EOS.
- Summary of CD4+, CD8+, CD4/CD8 ratio and Change from Baseline by Visit
    - This summary will include accumulated data through EOS.
- Summary of CD4+, CD8+, CD4/CD8 ratio and Percent Change from Baseline by Visit
    - This summary will include accumulated data through EOS.

6.1.3. Safety Analysis

All safety displays will be repeated and include all accumulated data through end of study.
For immunogenicity analysis, the frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by dose group. For the derivation of the overall assessment result for each participant, if all assessments for that subject are negative, then the subject is in negative category; Otherwise, if there are one or more assessments are positive, then the subject is in positive category. Titre value will be summarized by descriptive statistics (n, min, median, max) for each assessment time by dose group.

6.1.4. PK Analysis

All PK displays will be based on the PK population and will be similar as in the primary analysis with updated data.

6.1.5. Virology Analysis

The Virology displays will be based on safety population unless otherwise specified. The outputs will be similar as in the primary analysis with updated data.

6.1.6. Patient Reported Outcomes

Summary of acceptability of treatment questionnaire by treatment will be created with updated data.

6.2. Appendix 2 Abbreviations and Trademarks

6.2.1. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IP	Investigational Product
FAS	Full Analysis Set
OPS	Output and Programming Specification
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK

Abbreviation	Description
SAP	Statistical Analysis Plan
VLD	Viral load decline
CVF	Confirmed virologic failure
AUC	Area under curve

6.2.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
ACCEPT

7. REFERENCES

Arnould B, Gauchoux R, Meunier J, Gilet H, Regnault A. Validation of ACCEPT, a new generic measure to assess how patients with chronic diseases balance between the advantages and disadvantages of following the recommended treatment regimen in real-life. Value in Health 2013;16(7):A335.

Caskey, M, Klein, F, Lorenzi, J, Seaman, M, West, A, Buckley, N, et al. Viremia suppressed in HIV-infected humans by broadly neutralizing antibody 3BNC117. 2015. Nature. 522:487-491.

Caskey, M, Schoofs, T., Gruell, H., Settler, A, Karagounis, T., Kreider, E, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. 2017. Nature Medicine. 23:185-191.

Lynch, R.M., Boritz, E., Coates, E, DeZure, A., Madden, P., Costner, P., et al., Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med, 2015. 7(319): p. 319ra206.

Marant C, Spizak C, Longin J, Marrel A, Van Ganse E, Arnould B, Patrick DL. Development of the ACCEPT© questionnaire to assess acceptability of long term treatments: Qualitative steps. Value in Health 2009;12(7):A400.

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