Protocol

Study ID: 219239

Official Title of Study: A Phase 1, randomized, open-label, parallel group study to evaluate the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or prefilled syringe fitted with a safety syringe device in healthy adult participants

Date of Document: 26-Jul-2023

Clinical Study Protocol

Primary Study Intervention(s)	Bepirovirsen (GSK3228836)
Other Study Intervention(s)	Not Applicable
Study Identifier	219239
Approval Date	26 Jul 2023
Title	A Phase 1, randomized, open-label, parallel group study to evaluate the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or prefilled syringe fitted with a safety syringe device in healthy adult participants
Compound Number/Name	Bepirovirsen (GSK3228836)
Brief Title	A study to evaluate the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or prefilled syringe fitted with a safety syringe device in healthy adult participants
Sponsor	GSK Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Dickens Theodore, MD, MPH Group Senior Clinical Development Director

Medical monitor name and contact can be found in local study contact information document

Protocol 219239 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical and/or digital - informed consent of the participant and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

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Study identifier	219239
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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

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CCI [redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	Albumin to creatinine ratio
ADA	Anti-drug antibodies.
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransaminase
ANCA	Anti-neutrophil cytoplasmic antibodies
APTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC(0-inf)	Area under the concentration-time curve from time zero extrapolated to infinity
AxMP	Auxiliary medicinal product
C3/C4	Complement component 3/ Complement component 4
CA	Competent authority
CHB	Chronic hepatitis B
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CV	Coefficient of variation
CVb	Between subject coefficient of variation
DAIDS	Division of AIDS

Abbreviation	Definition
DIVI	Drug Induced Vascular Inflammation
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration, United States of America
GCP	Good clinical practices
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCP	Healthcare professionals
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICSR	Individual case safety reports
IEC	Independent ethics committee
IFU	Instructions for use
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational medicinal product

Abbreviation	Definition
NQ	Non-quantifiable
PCR	Polymerase chain reaction
PFS	Prefilled syringe
PK	Pharmacokinetic
PT	Prothrombin time
QTL	Quality tolerance limit
RPGN	Rapidly progressive glomerulonephritis
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome coronavirus
SoA	Schedule of activities
SOC	System organ class
SPEP	Serum Protein Electrophoresis
SRT	Safety Review Team
SSD	Safety syringe device
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
UPEP	Urine Protein Electrophoresis
USADE	Unanticipated serious adverse device effect
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Term	Definition
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
NIMP/AxMPAxMP	A NIMP or AxMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to

Term	Definition
	ensure that adequate medical care is provided for the participant during a study.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, randomized, open-label, parallel group study to evaluate the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or prefilled syringe fitted with a safety syringe device in healthy adult participants

Brief Title: A study to evaluate the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or prefilled syringe fitted with a safety syringe device in healthy adult participants

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.5.

1.2. Schema

Figure 1 Study Design Overview

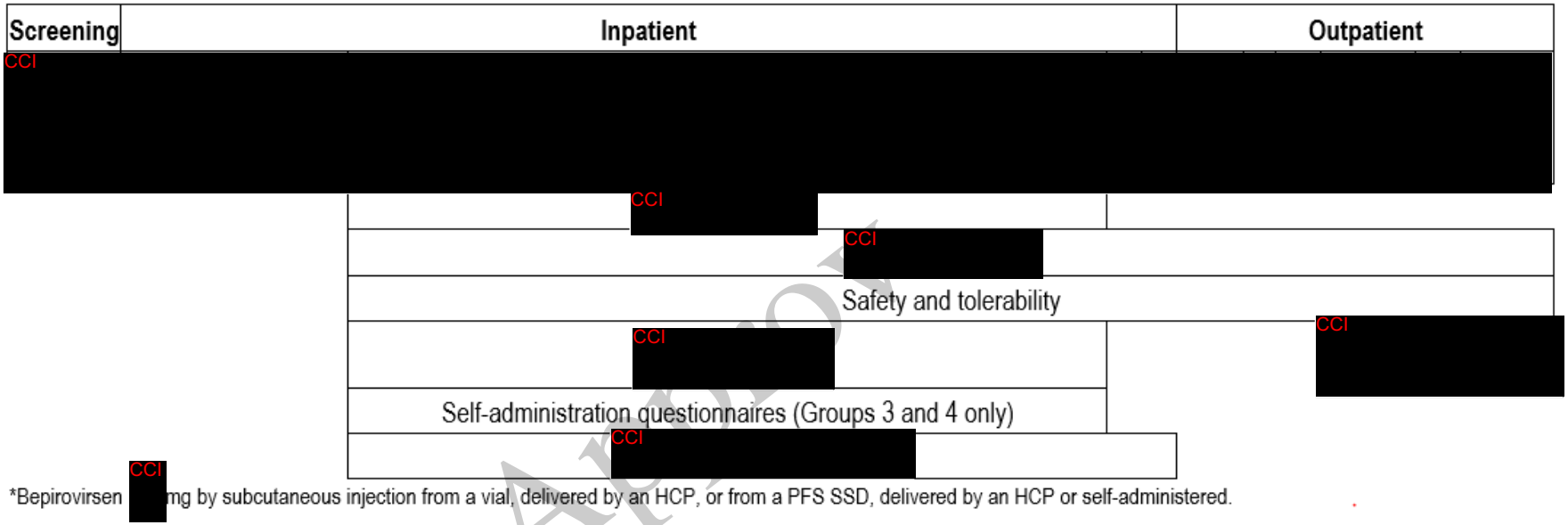
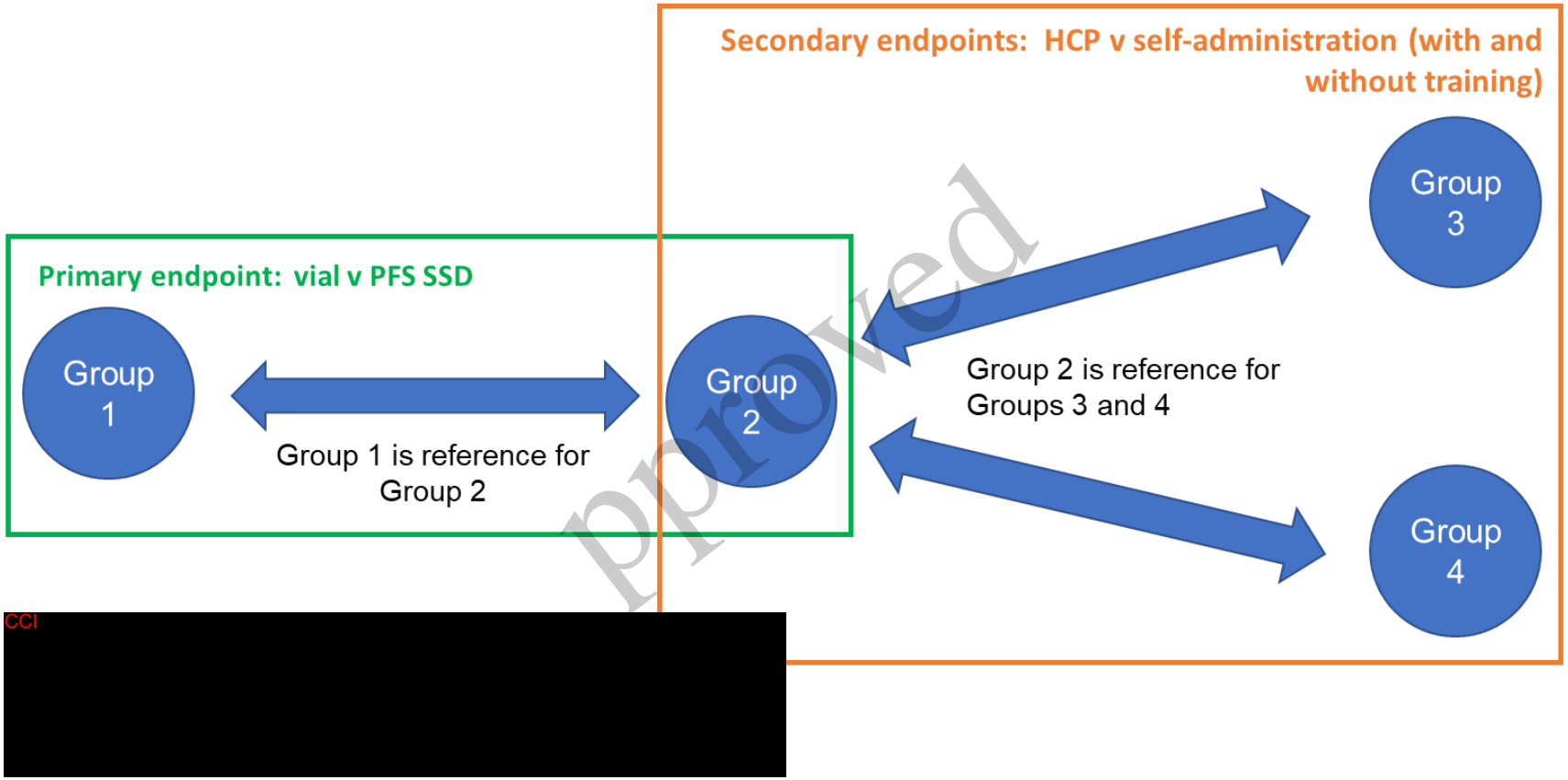


Figure 2 Study Design



Randomized 3:3:2:2 to Groups 1-4. Randomization schedule also includes injection site: upper arm, abdomen, or thigh (1:1:1) in Groups 1 and 2, and abdomen or thigh (1:1) in Groups 3 and 4. Recruitment into all groups to proceed in parallel.

1.3. Schedule of activities (SoA)

Table 1 Screening Visit

Procedure	Screening (up to 28 days before first dose)	Notes
Informed consent	X	
Inclusion and exclusion criteria	X	
Demography	X	
Past and current medical conditions	X	
Full physical examination including height and weight	X	At a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
Vital signs	X	Blood pressure and heart rate in triplicate; mean of 3 measurements used to confirm eligibility. Respiratory rate and temperature, single measurements.
COVID-19 test	X	Using a PCR or antigen test approved by the country regulatory authorities.
Human immunodeficiency virus, hepatitis B and C screening	X	If test otherwise performed within 3 months before first challenge day, testing at screening is not required.
Medication/drug/alcohol history	X	Includes substance usage and current medical condition.
Drug, alcohol, and cotinine screen	X	As per standard local practice.
12-lead ECG	X	In triplicate; mean of 3 measurements used to confirm QTc eligibility.
Follicle-stimulating hormone	X	As needed, to confirm postmenopausal status.
Serum pregnancy test	X	WOCBP only.
Clinical chemistry, hematology and urinalysis	X	
Urine ACR	X	
C3, C4, hs-CRP, p-ANCA, c-ANCA	X	MPO-ANCA and PR3-ANCA to be performed if p-ANCA or c-ANCA is positive.
Rheumatoid Factor	X	
Coagulation Panel (PT, INR, APTT)	X	
Alpha-fetoprotein (AFP)	X	
AE and SAE review	X	From signing consent. AEs and SAEs that occur prior to the first administration of IMP should be recorded only if assessed as related to study participation (e.g., protocol mandated procedures or invasive tests).
Prior medication	X	

ACR = Albumin to creatinine ratio. AE = adverse event. ANCA = Anti-neutrophil cytoplasmic antibodies. APTT = Activated partial thromboplastin time. C3/C4 = Complement. COVID-19 = Coronavirus disease 2019. ECG = electrocardiogram. hs-CRP = High-sensitivity C-reactive protein. IMP = Investigational medicinal product. INR = International normalized ratio. PCR = polymerase chain reaction. PT = Prothrombin time. SAE = serious adverse event. WOCBP = Woman of childbearing potential.

Table 2 Study Session to Final Visit and Early Withdrawal

Procedure	Day CCI Refer to Table 3 for acceptable time windows										Early withdrawal	Notes
Inpatient stay	<==========											
Outpatient visit					X	X	X	X	X	X	X	
Brief physical examination		X[1]	X[1]		X[1]	X	X	X	X	X	X	An interim symptom-targeted brief physical examination. [1]Within 1 h before dosing and at 24 and 72 h after dosing.
Vital signs	X	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	Blood pressure and heart rate in triplicate before dosing, and single measurements after dosing. Respiratory rate and temperature, single measurements at all time points. [2]Within 1 h before dosing and at 24, 48 and 72 h after dosing.
COVID-19 test	X											Using a PCR or antigen test approved by the country regulatory authorities. Test can be performed before Day –1 if required before admission for inpatient stay.
Drug, alcohol, and cotinine screen	X											As per standard local practice.
Safety 12-lead ECG	X	X[3]	X[3]	X[3]							X	In triplicate before dosing; single measurements after dosing. [3]Within 1 h before dosing and at 24 and 48 h after dosing.
Pregnancy test	X									X	X	Serum or urine. WOCBP only.
Clinical chemistry, haematology and urinalysis		X[1]	X[1]			X	X[4]	X[4]	X[4]	X	X	[1]Within 1 h before and at 24 and 72 h after dosing. [4]If results on Day 15 are within normal range, Day 29 and 43 tests are not required, and the next required time point is Day 64. If results on Day 15 are out of normal range, test should be repeated on Day 29; if results are still out of range on Day 29, test should be repeated on Day 43.
Urine ACR		X[5]	X[5]				X		X		X	[5]Within 1 h before and at 24 h after dosing.
C3, C4, hs-CRP, p-ANCA, c-ANCA		X[6]										[6]Within 1 h before dosing. Post-dose sample to be taken only if the investigator considered there was an event of vascular inflammation

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Procedure	Day										Early withdrawal	Notes
	CCI											
	Refer to Table 3 for acceptable time windows											
Coagulation Panel (PT, INR, APTT)		X[6]										[6]Within 1 h before dosing.
Randomization		X										
CCI dose of bepirovirsen		CCI										CCI
CCI												
Assessment of injection site		X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	[2]Within 1 h before dosing and at 24, 48 and 72 h after dosing.
CCI												
AE and SAE review	<==========											AEs and SAEs that occur prior to the first administration of IMP should be recorded only if assessed as related to study participation (e.g., protocol mandated procedures or invasive tests).
Prior/ concomitant medication review	<==========											

ACR = Albumin to creatinine ratio. AE = adverse event. ANCA = Anti-neutrophil cytoplasmic antibodies. APTT = Activated partial thromboplastin time. C3/C4 = Complement. COVID-19 = Coronavirus disease 2019. ECG = electrocardiogram. hs-CRP = High-sensitivity C-reactive protein. IMP = Investigational medicinal product. INR = International normalized ratio. PCR = polymerase chain reaction. PFS = prefilled syringe. PK = pharmacokinetic. PT = Prothrombin time. SAE = serious adverse event. WOCBP = Woman of childbearing potential

Table 3 Acceptable Visit/Time Point Windows

Assessment	Planned Timepoint	Acceptable window
Safety assessments*	Within 1 h before dosing	Within 90 min before dosing
	Up to Day 3	+/- 15 min
	Day 4	+/- 8 h
	Day 8 and 15	+/- 1 day
	Day 29 onwards	+/- 3 days
CCI [redacted]		

*Vital signs, 12-lead ECG, clinical laboratory tests, assessment of injection site

2. INTRODUCTION

2.1. Study rationale

The aim of this study is to provide relative bioavailability data to support the transition from the vial presentation of bepirovirsen, which is currently under investigation in the Phase 3 trials, to a ready-to-use liquid in a PFS fitted with an SSD. The study in healthy participants is intended to demonstrate comparable bepirovirsen pharmacokinetics of SC injections of:

- Vial and PFS SSD presentations, when administered by an HCP; and
- HCP administration and self-administration of the PFS SSD.

Safety and tolerability will also be assessed.

2.2. Background

HBV infection, especially chronic infection, is a significant worldwide medical problem. Globally, in 2019, an estimated 296 million people were living with chronic HBV infection. Viral hepatitis led to 1.34 million deaths and of these deaths, 66% were the result of complications of chronic HBV infection [WHO, 2017; WHO, 2021].

The goal of therapy for chronic HBV infection is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated liver disease, end stage-liver disease, HCC, or death. This goal can be achieved if HBV replication is suppressed in a sustained manner, thereby decreasing the histological activity of chronic HBV infection and reducing the risk of cirrhosis and HCC [Liaw, 2004; Feld, 2009]. In both HBeAg positive- and -negative chronic HBV infection, the ultimate treatment endpoint is loss of detectable serum HBsAg [Lok, 2017; EASL, 2017]. However, despite treatment with approved therapies, including nucleoside or nucleotide (nucleos(t)ide) analogue and/or pegylated interferon, rates of HBsAg loss following 12 months of treatment generally range- from 0% to 3% in most studies [Lok, 2017; EASL, 2017].

Bepirovirsen, an antisense oligonucleotide, was designed to inhibit the synthesis of HBV viral proteins. The binding site for bepirovirsen is present within all HBV mRNA and pgRNA. Bepirovirsen directly targets HBV RNAs via RNase H mediated degradation, resulting in the reduction of viral proteins, including HBsAg. Bepirovirsen treatment permits examination of reduction in serum levels (including HBsAg) and HBV RNA/DNA [Yuen, 2007]. Bepirovirsen allows resumption of a host immune response against HBV and infected cells and can induce HBsAg seroclearance.

Bepirovirsen Solution for Injection, CCI mg/mL is a single-use sterile liquid drug product supplied in a clear glass vial. A ready-to-use PFS assembled into an SSD has been developed which will be more convenient and may allow the ultimate goal of patient self-administration.

The formulation is unchanged between vial and safety syringe device. Consequently the likelihood of clinically significant differences in the systemic exposure, efficacy or safety profile is considered to be low. The relative bioavailability study will compare bepirovirsen exposures (AUC and Cmax) between vial and PFS SSD to ensure comparable PK exposures. The study will also compare bepirovirsen exposures between HCP administration and self-administration using the PFS SSD presentation.

A full description of the liquid drug product (vial and PFS SSD) is given in the Investigators' Brochure Supplement [GSK Document No.: RPS-CLIN-035276].

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of bepirovirsen may be found in the IB [GSK Document No.: RPS-CLIN-035276].

2.3.1. Risk assessment

Relevant risks associated with bepirovirsen treatment in this study are summarized in Table 4. A thorough description of all risks is included in the IB (Section 6). Additional monitoring for liver chemistry, DIVI, platelet count, renal function are discussed in Section 7.1. For a CCI dose administration of CCI mg, the risks are of low likelihood but cannot be ruled out.

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [Bepirovirsen]		
Non-clinical Risks:		
Drug Induced Vascular Inflammation (DIVI) and Complement Activation	Inflammatory and immune changes are recognized as a class effect of ASOs. Vasculitis and/or perivascular inflammation has been described in monkey studies with many, if not most ASOs. DIVI has not been observed in clinical studies with bepirovirsen to date.	**Laboratory Evaluations:** Inclusion of tests for biomarkers of inflammation/complement activation that would be expected to accompany vascular injury are to be taken at the time of a clinical event that is suggestive of vasculitis and/or immune activation and compared to referenced baseline measurements. A monitoring strategy is included (see Section 7.1.4)
Clinical Risks:		
Serious liver injury	The liver is a site of accumulation of ASOs. Liver findings in nonclinical studies of bepirovirsen were generally limited to mild hepatic enzyme elevations associated with hepatic vacuolation without concomitant histologic evidence of degeneration in mice, consistent with findings noted with other 2'-methoxyethyl (MOE) ASOs. Review of the	The risk of serious liver injury is very low after a single dose of bepirovirsen. Neverless, hepatic enzyme monitoring will be performed (see Section 7.1.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	available clinical data indicates liver enzymes are increased on treatment with ASOs (for treatment of diseases other than chronic HBV infection) in a low percentage of patients compared to placebo. A prior single dose study in healthy volunteers (213725) did result in an ALT increase > ULN in 1 participant treated with CCI mg bepirovirsen. This was not associated with other changes in liver chemistry (e.g., bilirubin, INR) and did not have a clinical consequence. Review of AE data and laboratory data in Phase 2a and Phase 2b studies in participants with CHB in which bepirovirsen was given weekly for 4 weeks and 24 weeks respectively and where ALT increases > 3xULN were observed, showed no evidence of DILI. CCI [redacted]	
Injection site reactions	ISRs have been reported with ASOs and reported in clinical studies with bepirovirsen. ISRs were the most common study treatment-related AEs with the majority reported as Grade 1 severity (mild). The majority of ISRs are reported as injection site erythema, injection site pain and injection site pruritus. Few events have led to treatment discontinuation.	Evaluations: Participants are assessed for ISRs at all visits as per the SoA.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood drawn	Risks with phlebotomy include bruising, bleeding, infection, and nerve damage.	Procedures to be performed by trained personnel (i.e., study nurse).
Handling and usage risks associated with PFS SSD	The IMP will be administered by or under the supervision of health care professionals. Anticipated device effects are nonserious, effects are unlikely, improbable, occasional, or remote and any effects are due to user errors.	Instructions for use on how to handle and use the devices will be provided.

2.3.2. Benefit assessment

As this Phase 1 study will be conducted in healthy adult participants, there will be no direct benefit to study participants included in this study.

Participants in this study will contribute to the development of an improved delivery of treatment for patients with CHB.

2.3.3. Overall benefit-risk conclusion

Whilst there is no benefit of treatment to the participant in this study, measures have been taken to minimize the participant's risk of participation.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objective(s)	Endpoint(s)
Primary	
• To estimate the relative bioavailability of vial and PFS SSD for a single dose of bepirovirsen delivered by SC injection by an HCP in healthy participants	• Cmax and AUC(0-inf) of bepirovirsen in plasma.
Secondary	
• To estimate the relative bioavailability of HCP administered vs self-administration following HCP training for a single dose of bepirovirsen delivered by SC injection in healthy participants	• Cmax and AUC(0-inf) of bepirovirsen in plasma.
• To estimate the relative bioavailability of HCP administered vs self-administration with no HCP training for a single dose of bepirovirsen delivered by SC injection in healthy participants	• Cmax and AUC(0-inf) of bepirovirsen in plasma.
Safety	
• To compare the safety and tolerability of CCI CCI of bepirovirsen CCI mg by randomized group.	• Occurrences of AEs and SAEs • Change from baseline at each time point in clinical laboratory tests and vital signs
Exploratory	
CCI [redacted]	

Primary estimand

The primary interest is to estimate the relative bioavailability, measured by Cmax and AUC(0-inf), following a CCI [redacted] of bepirovirsen via PFS SSD versus a vial in healthy adult participants.

The primary PK estimands are described by the following attributes:

- Population:

  Healthy male and female participants aged 18 to 55 years.

- Treatment Condition:

  CCI [redacted] of bepirovirsen injection administered via PFS SSD versus CCI [redacted] of bepirovirsen administered via a vial.

- Variables:

  AUC(0-inf) and Cmax.

- Summary measure:

  Ratio of geometric means of PFS SSD versus vials for Cmax and AUC(0-inf).

- Intercurrent Events:

  Use of prohibited medication. This intercurrent event is not expected to impact the PK of bepirovirsen so a treatment policy strategy will be used, and the individual PK concentrations after the occurrence of the intercurrent event will still be included in the PK analysis.

  Participants who did not receive CCI the injections and had an incomplete or erroneous dosing. A principal stratum strategy policy will be used, where the strata of interest is the group of participants who are able to receive the complete dose.

  A supplemental estimand will also be analyzed as per the primary estimand, except for the intercurrent event of incomplete dosing will use a treatment policy strategy.

Secondary estimand(s)

The secondary interest is to estimate the relative bioavailability, measured by Cmax and AUC(0-inf):

1. Following a CCI f bepirovirsen via PFS SSD versus self-administration of a single dose of bepirovirsen with HCP training
2. Following a CCI of bepirovirsen via PFS SSD versus self-administration of a single dose of bepirovirsen with no HCP training.

The secondary PK estimands are described by the following attributes:

- Population:

  Healthy male and female participants aged 18 to 55 years.

- Treatment condition:

  CCI dose of bepirovirsen administered via PFS SSD versus self-administration of a single dose of bepirovirsen with HCP training.

  CCI dose of bepirovirsen administered via PFS SSD versus self-administration of a single dose of bepirovirsen with no HCP training.

- Variables:

  AUC(0-inf) and Cmax.

- Summary measure:

  Ratio of geometric means of PFS SSD versus self-administration with HCP training and with no HCP training for Cmax and AUC(0-inf).

- Intercurrent Events:

  Use of prohibited medication. This intercurrent event is not expected to impact the PK of bepirovirsen so a treatment policy strategy will be used, and the individual PK concentrations after the occurrence of the intercurrent event will still be included in the PK analysis.

  Participants who did not receive CCI the injections and had an incomplete or erroneous dosing. A principal stratum strategy policy will be used, where the strata of interest is the group of participants who are able to receive the complete dose.

  Supplemental estimands will also be analysed as per the secondary estimand, except for the intercurrent event of incomplete dosing will use a treatment policy strategy.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 1, open-label, randomized study to investigate SC bepirovirsen when delivered via SC injection from vial or PFS SSD in healthy adult participants. The study will assess relative bioavailability, safety and tolerability, as well as the usability of the PFS SSD for self-administration.

A total of approximately CCI participants will each complete a single study session, in a parallel design, and will each take up to CC weeks to complete the study.

Participants will be screened within 28 days before dosing. They will attend the clinical unit the day before dosing (Day –1) and will remain inpatient until 2 days after dosing

(Day 3). They will receive bepirovirsen CCI mg as CCI mg SC injections on Day 1, randomized 3:3:2:2 to:

CCI

CCI

The randomization will be stratified by body weight (CCI . The site of injection will be randomized in a 1:1:1 ratio to the upper arm, abdomen, or thigh in Groups 1 and 2, and in a 1:1 ratio to abdomen or thigh in Groups 3 and 4.

Participants will return for outpatient visits on Days CCI

Blood samples will be taken to measure levels of bepirovirsen and ADAs against bepirovirsen, and safety and tolerability will be assessed from before dosing and until the final visit. The observing HCP and participants in Groups 3 and 4 will complete questionnaires, respectively, during and after dosing, to assess usability of the PFS SSD for self-administration. Blood samples will also be taken for biomarker analysis before dosing and up to 48 h after dosing.

The study design schematic is presented in Section 1.2.

4.2. Scientific rationale for study design

Conducting the study in healthy participants mitigates the recruitment and patient burden limitations with administering a single dose of bepirovirsen to CHB patients. A population of healthy participants is frequently used in the assessment of the relative bioavailability of both small and large molecules. In addition, healthy participants are a suitable population for biopharmaceutical PK comparability studies, and the data can be extrapolated to other populations. In addition, usability of the PFS SSD can be reliably assessed in healthy participants via questionnaires to support design of the human factors summative evaluation.

CCI
.

Bepirovirsen has a half-life of approximately CCI in healthy subjects. A CCI

A CCI dose of bepirovirsen will be administered as CCI injections at 1 of 3 injection sites (upper arm, abdomen, or thigh) when administered by an HCP, or at 1 of 2 injections sites (abdomen or thigh) when self-administered. Upper arm is not a feasible administration site for self-administration. To prevent bias and maintain balance in treatment groups, the injection site will be randomized in addition to the randomization for device. To minimize the impact of potential confounding factors and variability, the randomization will also be stratified by body weight as this has been associated with bepirovirsen exposure.

Collection of PK blood samples up to Day CC will ensure that the bepirovirsen plasma concentration-time profile is well described with the extrapolated portion of AUC(0-inf) below CCI

The study will be open-label. This is acceptable because the primary and secondary endpoints are PK parameters, which are not subjective measures. Any potential for selection bias will be reduced by central randomization.

4.2.1. Participant input into design

Participant input into the study design is not deemed necessary for this Phase 1 clinical pharmacology study.

4.3. Justification for dose

A CCI of bepirovirsen CCI mg will be administered as CCI mg SC injections provided as vials or PFS SSD on Day 1. CCI [redacted].

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, ECGs and vital signs.
WEIGHT
3. Body weight ≥50 kg and body mass index (BMI) within the range 19 to 29.9 kg/m^2 (inclusive).
SEX
4. Male and/or female. a. There are no contraceptive requirements for male participants. b. A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies: • Is a WONCBP as defined in the protocol (Section 10.4) OR • Is a WOCBP and using a contraceptive method (for a period of 28 days before dosing) that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 of the protocol during the study intervention period and for at least 7 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. • If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions
1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
2. Abnormal blood pressure as determined by the investigator.
3. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Participants with signs or symptoms suggestive of COVID-19 (e.g., fever, cough) within 14 days of inpatient admission.
5. Participants with any other medical conditions which, in the judgement of the investigator and Medical Monitor, could jeopardize the integrity of the data derived from that participant or the safety of the participant.
6. Platelets <$140x10^9$/L.
7. ALT >1.5xULN
8. Total bilirubin >1.5xULN (isolated total bilirubin >1.5xULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
9. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. QTcF >450 msec.
Prior/Concomitant Therapy
11. Past, current or intended use of over-the-counter or prescription medication [including herbal medications] within 7 days or 5 half-lives (whichever is longer) before dosing [Specific medications listed in Section 6.9 of the protocol may be allowed].
12. Current or prior use of creatine-containing supplements and intended use up to 50 days post-dosing.
13. Prior use of immunosuppressive drugs within 3 months before dosing or interferon within 12 months before dosing.
14. Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months before dosing.

Prior/Concurrent Clinical Study Experience
15. Loss of blood or blood products in excess of 500 mL within any 3-month period during the study.
16. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
17. Current enrollment or past participation in another investigational study in which an investigational intervention (e.g., drug, vaccine, invasive device) was administered within 5-half-lives (if known) or twice the duration of biological effect (if known), whichever is longer, or within the last 90 days (if half-life and duration of biological effect are unknown), before the first dosing day in the current study.
18. Current enrollment or past participation in this clinical study.
Diagnostic Assessments
19. Presence of HBsAg at screening or within 3 months before dosing.
20. Positive hepatitis C antibody test result at screening or within 3 months before dosing. NOTE: Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.
21. Positive hepatitis C RNA test result at screening or within 3 months before dosing. NOTE: Test is optional and subjects with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
22. Positive pre-study drug/alcohol screen, including THC.
23. Positive HIV antibody test.
24. Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
25. A positive test for active COVID-19 infection at or before admission for the inpatient stay. The testing should be done using a molecular polymerase chain reaction (PCR) or antigen test approved by the country regulatory authorities.
Other Exclusion Criteria
26. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >14 units for males or females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
27. Regular use of known drugs of abuse, including THC.
28. History of sensitivity to bepirovirsen or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor contraindicates their participation.

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

No restrictions.

5.3.2. Caffeine, alcohol, and tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 2 hours before the start of dosing until 1 hour after dosing.
- Participants will abstain from alcohol for 24 hours before admission until discharge from the clinical unit.
- Use of tobacco- and nicotine-containing products is not allowed from 6 months prior to screening until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise (exertion requiring maximum physical effort/strength) for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (e.g., watching television, reading).

5.3.4. Other restrictions

Participants will be asked to refrain from donating blood for the duration of their study participation.

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened unless discussed and agreed with the Medical Monitor. Individuals who fall out of the screening window, may be rescreened at the discretion of the investigator.

5.5. Criteria for temporarily delaying

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol, and further details in Table 5.

6.1. Study intervention(s) administered

Table 5 Study Intervention(s) Administered

Intervention Label	Open Label	Open Label
Intervention Name	Bepirovirsen, (GSK3228836)	Bepirovirsen, (GSK3228836)
Intervention Description	Bepirovirsen solution for injection, CCI mg/mL packaged in a vial. CCI [redacted] required to deliver CCI mg dose.	Bepirovirsen solution for injection, CCI mg/mL packaged in a PFS fitted with a PFS SSD. CCI [redacted] required to deliver CCI mg dose.
Type	Drug	Drug
Dose Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)	CCI mg/mL	CCI mg/mL
Dosage Level(s)	CCI mg	CCI mg
Route of Administration	SC Injection	SC Injection
Use	Experimental	Experimental
IMP and NIMP/AxMP.	IMP	IMP
Sourcing	Supplied by GSK	Supplied by GSK
Packaging and Labeling	Study intervention will be provided in a carton with an insert. Each carton will be labeled as required per country requirement.	Study intervention will be provided in carton with an insert. Each carton will be labeled as required per country requirement.

Bepirovirsen Solution for Injection, CCI mg/mL, is a clear, CCI [redacted] solution, essentially free from visible particles. Bepirovirsen vial is presented as a 1 mL nominal fill volume of Bepirovirsen Solution for Injection CCI mg/mL in a CCI mL clear glass vial, closed with a CCI [redacted] rubber stopper and sealed with aluminium overseal with removeable plastic cap.

The drug product is administered as CCI SC injections to deliver the clinical dose of CCI mg. It is recommended to use 27G thin-wall needles or 25G regular-walled needles for injection.

The PFS SSD is a medical device and is described in Section 6.1.1.

6.1.1. Medical devices

Bepirovirsen PFS SSD is a single use, prefilled, disposable device intended to enable manual delivery of the drug product while providing a needle shielding feature (post-use) and enhanced ergonomics. CCI [redacted]

CCI [redacted]

CCI [redacted]

- Instructions for medical device use are provided CCI [redacted]
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.7 and Section 10.6) and appropriately managed by GSK.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff or HCP may supply, prepare, or administer study intervention (see Section 4.1).
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Assignment to study intervention

Study intervention will be dispensed on Day 1 as summarized in the SoA (Section 1.3).

The GSK Randomization Officer will use the Randall NG system to generate a randomization schedule.

With central randomization, knowledge of the randomized treatment group for previous participants does not predict which treatment group will be assigned to the next randomized participant.

Randomization and study intervention assignment will be facilitated by the IRT through the central RAMOS NG system.

Following confirmation of fulfilment of study entry criteria, study site personnel will be required to register participants using RAMOS NG for assignment of a unique identifier which comprises of 4 digits (e.g., 1 001 and increasing) designating each participant's randomization code and treatment sequence assignment.

Prior to first dosing of each group, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 4 treatment sequences of the study, according to the randomization schedule.

6.4. Randomization

This is an open-label study; Any potential for selection bias will be reduced by central randomization.

A single randomization schedule will randomly assign participants pre-dose to treatment group and injection site according to the ratios shown in Table 6.

Additionally, randomization will be stratified by body weight (CCI [redacted]).

Table 6 Randomization Schedule

	Injection Site			Total
Group	Arm	Thigh	Abdomen	
1	1	1	1	3
2	1	1	1	3
3		1	1	2
4		1	1	2

6.5. Study intervention compliance

All participants will be dosed at the clinical site, where they will receive study intervention directly from the investigator or designee, or they will self-administer the medication provided, under medical supervision. The date and time of each dose administered in the clinic 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.

6.6. Dose modification

This is a CCI [redacted] study in which dose modification is not permitted.

6.7. Continued access to study intervention after the end of the study

Not applicable.

6.8. Treatment of overdose

For this study, any dose of bepirovirsen greater than CCI [redacted] mg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose. In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until the study intervention can no longer be detected systemically (at least 50 days).

Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF).

6.9. Prior and concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor, if required.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL-

7.1. Discontinuation of study intervention

Discontinuation of study intervention is not applicable in this study, as it is a single dose by design. Monitoring criteria are outlined in the section below.

7.1.1. Liver chemistry monitoring criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology. Although stopping criteria for continued dosing of study intervention are not applicable for single dose studies, if participants are found to have values consistent with usual stopping parameters, it is appropriate to institute evaluation and monitoring criteria according to standard GSK criteria. Therefore, liver function tests should be evaluated according to stopping criteria and safety follow-up procedures/tests as specified in Appendix 6 should be instituted if defined parameters are reached.

For ALT values ≥3xULN:

- See Appendix 6

- if possible Hy's Law case: ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct) or INR>1.5, report as an SAE

7.1.2. Hematological monitoring criteria

Platelet counts must be re-checked as soon as possible (with a new blood sample) if the platelet count is uninterpretable, below the LLN reference range for healthy participants, or the sample shows platelet clumping.

Monitoring criteria are shown in Table 7

Participants with platelet counts <75x10^9/L will undergo further assessment including, but not necessarily limited to, anti-platelet antibodies. Monitor until platelet abnormalities resolve, stabilize, or return to within baseline values.

After the dose is administered, if a participant develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible.

Table 7 Hematological Monitoring Criteria

Platelet Count Value	Monitoring
75x10^9/L ≤ platelets <100x10^9/L	Monitor weekly until ≥100x10^9/L
50x10^9/L ≤ platelets <75x10^9/L	Assess anti-platelet antibodies Monitor every 2 to 3 days until 3 successive measurements ≥75x10^9/L, then weekly until ≥100x10^9/L
<50x10^9/L	Assess anti-platelet antibodies Monitor daily until >25x10^9/L, then every 2 to 3 days until 3 successive measurements ≥75x10^9/L, then weekly until ≥100x10^9/L

7.1.3. Drug induced kidney injury (renal) monitoring

If any of the following are observed, results should be confirmed (with a new blood sample), and if confirmed, further evaluation for alternative causes should be pursued in consultation with the Medical Monitor:

- Persistent uACR >0.3 mg/mg (>300 mg/g)
- Blood in urinalysis >5 red blood cells per high power field confirmed by urine microscopy (unless there is a known cause [e.g., females during menstruation])
- Gradual and consistent reductions of eGFR compared with baseline.

Following confirmation of the criteria above, if underlying cause other than drug-induced renal injury is not confirmed, further evaluation may include but not be limited to a 24 hour urine analysis, consultation with a nephrology specialist, renal ultrasound, urine microscopy, serum urea and creatinine, platelet count, urgent serum vasculitis screen (including ANCA, ANA, dsDNA, Rheumatoid Factor, cryoglobulins), SPEP/UPEP, and complement panel (C3, C4, C5a and Bb). Further evaluation and actions should be determined by the investigator in consultation with the Medical Monitor.

Participants must be monitored weekly until uACR or eGFR resolve, stabilize, or return to within baseline values.

If acute glomerulonephritis is confirmed or probable [i.e., meets clinical definition of RPGN if biopsy not feasible], delay in treatment of suspected RPGN should be avoided.

7.1.4. Drug induced vascular injury and complement activation

If the participant develops signs/symptoms of potential complement activation/DIVI including (but not limited to) new onset: persistent joint pain not resolved with simple analgesia, peripheral neuropathy, vasculitis/purpuric rash, signs of renal involvement, for example (haematuria; increasing presence of blood on urine microscopy, increasing urine ACR, rising creatinine, falling GFR), jaundice, haemolysis and/or thrombocytopenia, in addition to relevant investigations based on the participant's symptoms and signs, the following tests should also be conducted: C3, C4, Factor Bb, C5a, Rheumatoid factor, cryoglobulins (locally if available), ANCA, SPEP, UPEP, hs-CRP and compared to baseline values, if available.

Additional complement analyses for example CH50, Factor Bb level, Factor H level, sC5b-9 and samples for MCP-1 should also be considered in discussion with the Medical Monitor (who may consult with the internal Safety Panels).

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the CRF/eCRF for reasons including, but not limited to the list below:

Reasons	Additional items/Sub-reasons
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify
Physician Decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	Specify
Withdrawal by Participant	Burden of Procedure Participant Relocated Other
Death	Specify

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE as per instructions in Section 10.3.4.5.

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical history

The participant's medical history will be obtained by interviewing the participant and/or review of the participant's medical records. Any pre-existing conditions, signs and/or symptoms present prior to study start will be recorded in the eCRF.

8.2. Efficacy assessments

Not applicable for this study.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3). Additional time points for safety tests (such as vital signs, physical examinations, and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.3.1. Physical examination/history directed physical examination

- At screening, a complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Symptoms directed examination will be conducted at all other time points.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Injection site reactions

- Injection site reactions are any experiences which occur at the site of injection of the study treatment. Participants will be monitored closely for ISRs and ISRs should be recorded as AEs on a specific ISR eCRF page.
- Injection site reactions will be graded according to the criteria provided in the DAIDS grading table (see Appendix 7).

8.3.3. Vital signs

- Temperature, heart rate, respiratory rate, and blood pressure will be assessed as outlined in the SoA (Section 1.3).
- Blood pressure and heart rate measurements should be assessed in semi supine position (preferred, but not required) with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones)
- For triplicate blood pressure and heart rate measurements before dosing, 3 consecutive readings will be recorded at intervals of at least 1 minute. The full set of triplicates should be completed within a 5-minute recording period. The average of the 3 readings will be recorded.
- Vital signs should be taken before blood collection for laboratory tests.

8.3.4. Electrocardiograms

- 12-lead ECGs will be obtained as outlined in the SoA (Section 1.3), using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Manual calculation, if an automatic calculation is not available, is acceptable.
- For triplicate measurements before dosing, 3 consecutive readings will be recorded at intervals of at least 1 minute. The full set of triplicates should be completed within a 5 minute recording period. The average of the 3 readings will be recorded.
- ECGs should be taken before blood collection for laboratory tests.

8.3.5. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Clinically significant

abnormal laboratory findings are those judged at investigator discretion based on being more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significantly abnormal by the investigator or Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the Sponsor notified.
    - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.6. Pregnancy testing

- Female participants of childbearing potential must perform a screening serum pregnancy test, and a serum or urine pregnancy test on admission to the clinical unit, before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.4. Adverse Events (AEs) serious adverse events (SAEs), and other safety reporting

The definitions of AEs or SAEs can be found in Section 10.3 (Appendix 3).

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

- All AEs and SAEs will be collected from the signing of the informed consent until the final follow-up visit at the time points specified in the SoA (Section 1.3).

However, AEs and SAEs that occur prior to the first administration of IMP should be recorded only if assessed as related to study participation (e.g., protocol mandated procedures or invasive tests).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.4.5 and/or Section 10.6.4.4.

8.4.4. AESIs

8.4.4.1. ALT increases

The liver is a site of accumulation of ASOs and this has been exploited in the treatment of liver related diseases. ALT increases to levels > ULN were observed in healthy participants. These were not associated with concurrent symptoms or increases in bilirubin levels and all ALT increases returned to baseline levels during post-treatment follow-up.

A monitoring strategy for ALT is presented in Section 7.1.1.

8.4.4.2. Vascular Inflammation and complement activation

Inflammatory and immune changes are recognized as a class effect of ASOs. Despite the low risk for ASO-related vascular AEs in participants, the nature of the toxicity demands a conservative approach to care and monitoring to ensure the safety of participants.

A monitoring strategy is presented in 7.1.4

8.4.4.3. Thrombocytopenia

Thrombocytopenia, decreased platelets, is a well-recognized toxicity associated with ASOs and is monitorable in the clinic. Two types of thrombocytopenia have been described by the FDA amongst the 2-MOE ASOs. One type is a rapid onset, unpredictable thrombocytopenia that may present with mild or moderate bleeding, however, catastrophic, fatal bleeding can occur. The other more common type is characterized by a gradual decline in platelets leading to mild to severe thrombocytopenia and can be asymptomatic or associated with mild to severe bleeding.

A monitoring strategy of platelet count is presented in Section 7.1.2

8.4.4.4. Renal Injury

Glomerulonephritis, including rapidly progressing glomerulonephritis, has been reported with ASOs and is thought to be a result of the proinflammatory effect of ASOs. Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, is thought to sometimes lead to increased tubular proteinuria (as described in preclinical studies). Increases in urine protein have been described in the clinic.

A monitoring strategy of renal function (e.g., serum creatinine, ACR) is presented in Section 7.1.3

8.4.5. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs/ the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.4.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 8 Timeframes for Submitting SAE and Pregnancy Reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	electronic AEs Report	24 hours*	electronic AEs Report
Pregnancies	24 hours*	paper pregnancy notification report	24 hours *	paper pregnancy follow-up report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until no longer than 6 to 8 weeks following the estimated delivery date.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. See **Table** 8 for reporting timeframes.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.7. Contact information for reporting SAEs and pregnancies

Table 9 Contact Information for Reporting SAEs and Pregnancies

Study contact for questions regarding SAEs, pregnancies and SAEs linked to device deficiencies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs, pregnancies and SAEs linked to device deficiencies Available 24/24 hours and 7/7 days For medicines: uk.gsk-rd-gcsp-ctsm-admin@gsk.com

8.4.8. Medical device deficiencies

Medical devices (PFS SSD) are being provided for use in this study as the study intervention from Groups 2 to 4. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.8.3. Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email to gsk-rd.complaints@gsk.com and also to OAX37649@gsk.com if there is an associated SAE. If email is unavailable, then fax +44(0)20 8181 4780 should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.8.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

Blood samples for pharmacokinetic analysis of bepirovirsen will be collected at the time points indicated in SoA (Section 1.3). Each PK sample must be collected as close as possible to the planned time relative to when the dose is administered to the participant (which is 0 hour on Day 1). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Each blood sample will be processed into plasma and divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. PK samples will be analyzed using an appropriately validated assay by or under the supervision of the Sponsor.

Processing, storage and shipping instructions/procedures are provided in the Laboratory Manual.

8.6. Pharmacodynamics

Not applicable for this study.

8.7. Genetics

Not applicable for this study.

8.8. Biomarkers

- Blood samples (including serum and plasma) may be used to evaluate pharmacodynamic responses and assays related to the pathogenesis of chronic HBV infection and the participant's response to bepirovirsen.
- CCI [redacted]. Samples will be collected according to the schedule described in the SoA and as detailed in the laboratory manuals provided separately to sites.
- GSK may store samples for up to 20 years after the end of the study to achieve study objectives. The archived samples may be used as backup for assessments pre-specified in protocol CCI [redacted]

- Additionally, with participants' consent, samples may be used for further research by the GSK or others such as universities or other companies to contribute to the understanding of chronic hepatitis B or other diseases, the development of related or new treatments or research methods.
- Additional details of biomarker analysis will be provided in the biomarker analysis plan and the results will be documented in a separate report.

CCI [redacted]

CCI [redacted] CCI [redacted]

CCI [redacted]

CCI [redacted]

8.10. Health economics or medical resource utilization and health economics

Not applicable for this study.

CCI [redacted]

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

The SAP will include a more technical and detailed description of the statistical analysis described in this section. This section is a summary of the planned statistical analysis of the most important endpoints including primary and secondary endpoints.

9.1. Statistical hypotheses

This study is designed to estimate the relative bioavailability of a single dose of bepirovirsen administered SC from vial and PFS SSD presentations by a HCP in healthy participants. For Cmax and AUC(0-inf), point estimates and corresponding 2-sided 90% CIs will be constructed for the ratio of the geometric mean of the vial to the PFS SSD.

An additional assessment will be made by comparing the CCI [redacted] reference range of 0.8 to CCI [redacted]

9.1.1. Multiplicity Adjustment

No multiplicity adjustment will be implemented because the primary objective is to estimate the relative bioavailability of a CCI [redacted] of bepirovirsen, and no formal hypotheses will be tested.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure). • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study.	• Study Population
Safety	• Participants who received study intervention • Participants will be analyzed according to the study intervention administered.	• Safety
PK concentration	• All participants in the Safety analysis who received CCI the injections and had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	• PK concentration
PK Parameter	• All participants in the PK concentration population for whom valid and evaluable plasma PK parameters are derived. This primary analysis population will be used in the assessment and characterization of PK parameters (summary and analysis tables and figures).	• PK parameter

9.3. Statistical analyses

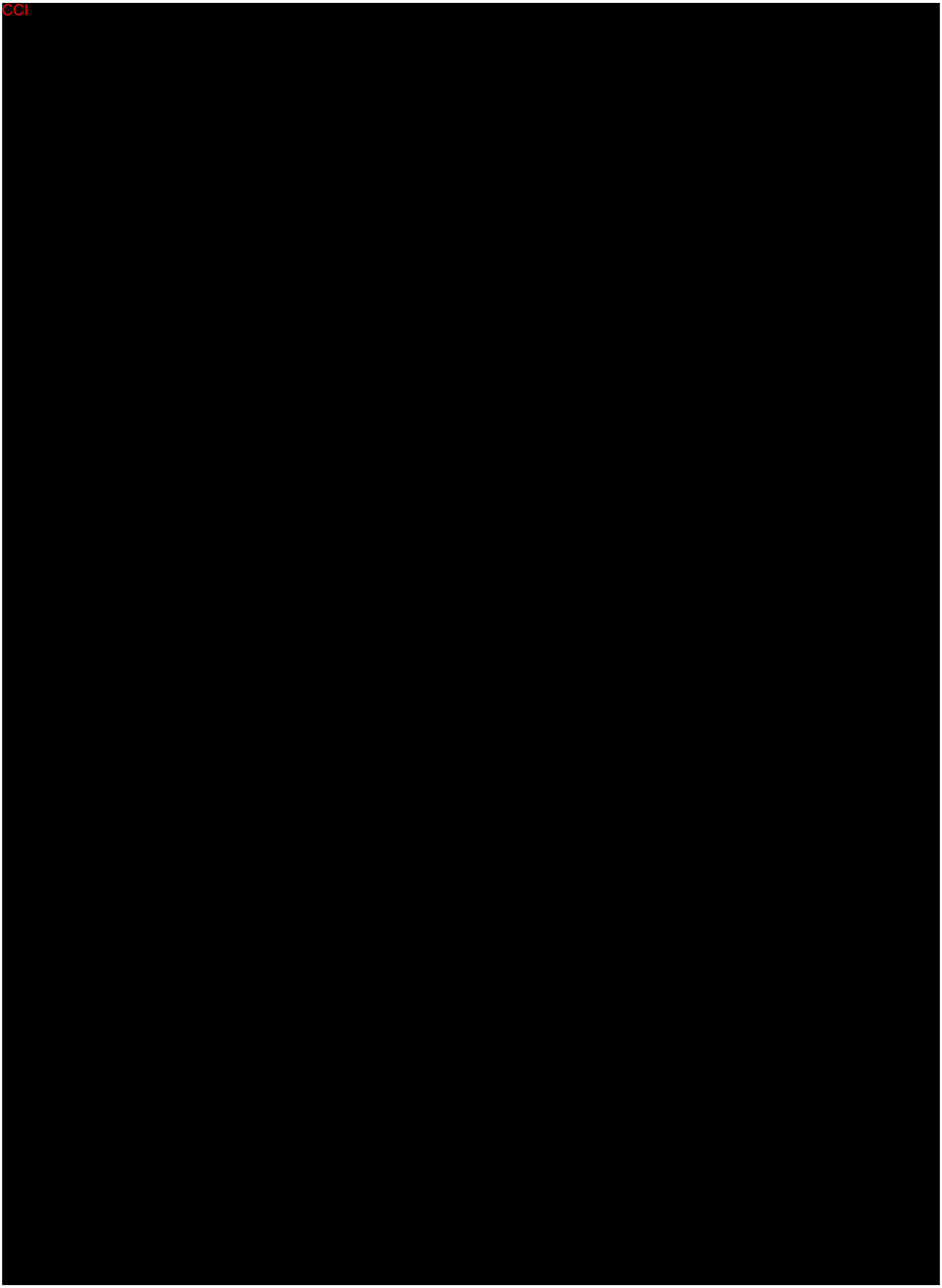
9.3.1. General considerations

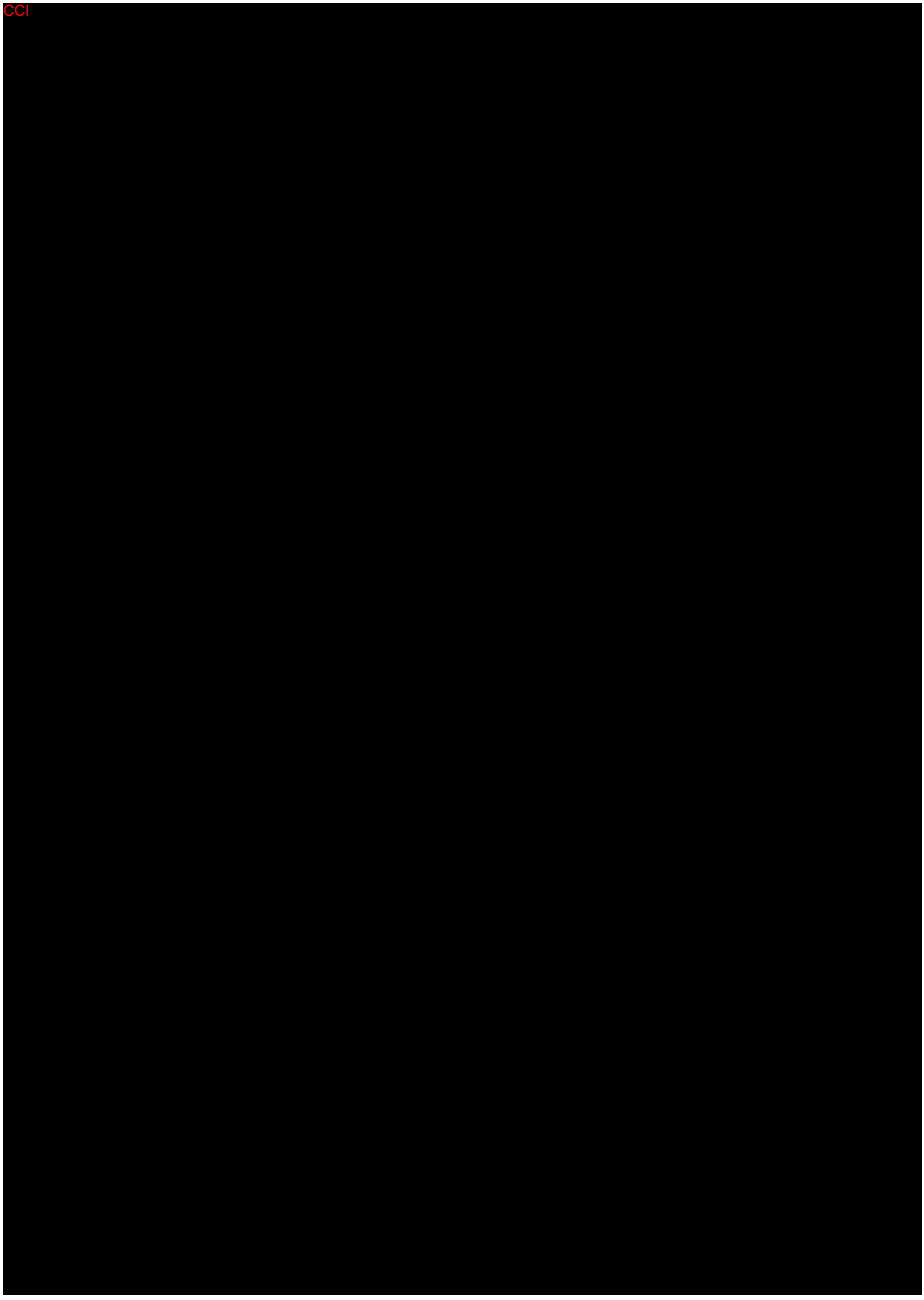
Based on the individual concentration-actual time data, the following PK parameters will be estimated by non-compartmental methods with SMS2000.

Parameter	Description
AUC(0-inf)	Area under the concentration-time curve from time zero extrapolated to infinity
Cmax	Maximum observed plasma concentration

PK data will be presented in graphical and/or tabular form and will be listed and summarized descriptively by treatment group, weight category and injection site.

CCI





To assess the secondary objectives of estimating relative bioavailability of group 2 compared to Groups 3 and 4, approximately CCI subjects will be randomized into Groups 3 and 4 (approximately CCI per arm). This will provide the same number of subjects in the applicable sites of administration (thigh and abdomen) compared to Groups 1 and 2.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, IFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees structure

An internal SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data agreement.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and site start and closure

Start of study and first act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in **Table** 11 will be performed by the central laboratory.
- Outside of specific protocol-defined tests, local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 11 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH	WBC count (with Differential if WBC abnormal): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase	Total, indirect, and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• By dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle-stimulating hormone • Serology (HIV antibody, HBsAg, HBcAb) • Highly sensitive urine or serum hCG pregnancy test (as needed for women of childbearing potential)[1] • Other laboratory: Coagulation Panel (PT, INR, APTT), Alpha-fetoprotein, p-ANCA, c-ANCA (MPO-ANCA, PR3-ANCA)[2], Complement factors C3, C4, Rheumatoid factor, hs-CRP • Urine ACR • SARS-CoV2 PCR or rapid antigen test[3] • Drug, alcohol and cotinine screen			
Additional tests listed under	Liver Chemistry Stopping Criteria[4] • Viral hepatitis serology (Hepatitis A IgM; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody, EBV capsid antigen IgM antibody (or if			

safety follow-up processes	unavailable, heterophile antibody or monospot testing); hepatitis E IgM antibody) • PK sample • Serum creatine phosphokinase and LDH. • Fractionate bilirubin, Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay
	Drug Induced Vascular Injury and Complement Monitoring Criteria • CH50 • Factor Bb level • Factor H level • sC5b-9 • cryoglobulins[5] • SPEP, UPEP • hs-CRP
	Hematological Monitoring Criteria • anti-platelet antibodies
	Drug Induced Kidney Injury Monitoring Criteria • 24-hour urine analysis • renal ultrasound • urine microscopy • serum urea and creatinine • platelets • urgent serum vasculitis screen (including ANCA, ANA, dsDNA, cryoglobulins[5]) • SPEP/UPEP • complement panel (C3, C4, C5a, and Bb)

NOTES:
1. Urine testing will be standard for the protocol unless serum testing is specified in the SoA, required by local regulation or IRB/IEC, or if urine testing is unavailable
2. MPO-ANCA and PR3-ANCA to be performed if p-ANCA or c-ANCA is positive.
3. Using PCR or antigen test approved by the country regulatory authorities
4. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver monitoring event are given in Section 7.1.1. All events of ALT≥3×ULN and bilirubin ≥2×ULN (≥35% direct bilirubin) or ALT≥3×ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
5. Cryoglobulins to be tested locally if available

Note: The investigator must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations: • Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

○ Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.4. Recording, assessment and follow-up of AE, SAE, and pregnancies

10.3.4.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the sponsors /required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, SAE and device deficiency reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.4.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.4.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESI (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until the event is resolved, stabilized, otherwise explained or until the participant is lost to follow-up.

Follow-up during the study

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.4.7.

10.3.4.6. Updating of SAE and AESI information after removal of write access to the participant's eCRF

When additional SAE and AESI information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.7).

10.3.4.7. Reporting of SAEs, AESIs and pregnancies

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.7.

SAE Reporting to the sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal)

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of

the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly effective methods[b] that are user dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 6: Liver safety: suggested actions and follow-up assessments

Liver chemistry monitoring criteria:

Liver chemistry monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

The procedures listed below are to be followed if a participant meets liver chemistry criteria as specified in Section 7.1.1:

- Notify the Medical Monitor within 24 hours of learning of the abnormality
- Complete the Liver Event CRF.
- Complete the "Safety Follow-up Procedures" listed below.
- Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see Monitoring)

Monitoring:

If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours
- Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

If ALT≥3xULN AND total bilirubin <2xULN and INR ≤1.5:

- Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24-72 hours
- Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline

Safety Follow-up Procedures for Participants who Meet *any* of the criteria:

Viral hepatitis serology including:

- Hepatitis A IgM antibody;
- HBsAg;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody;
- Hepatitis C virus RNA load;
- Hepatitis D virus antibody.

- Obtain a blood sample for PK analysis as soon as possible following the occurrence of an event. Record the date/time of the PK blood sample collection and the date/time of the last dose of study treatment prior to blood sample collection on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. Instructions for sample handling and shipping are included in the Laboratory Manual.
- Serum creatine phosphokinase and LDH.
- Fractionate bilirubin, if total bilirubin ≥1.5x ULN
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) as relevant on the Liver Event CRF.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
    - Record alcohol use on the Liver Events CRF.

The following are required for participants who meet the ALT and bilirubin criteria: ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5.

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]), if available.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) or Liver biopsy to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

10.6. Appendix 7: Medical device AEs, ADEs, SAEs, sADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in

users or other persons, which only include events related to investigational devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A Medical Device SAE is any serious AEs that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report/ IB (see Section 2.3).

10.6.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.6.4. Recording and follow-up of medical device AE and/or SAE and device deficiencies

10.6.4.1. Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Sponsor's AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.6.4.2. Assessment of intensity

Refer to Section 10.3.4.2

10.6.4.3. Assessment of causality

Refer to Section 10.3.4.3

10.6.4.4. Follow-up of medical device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.6.5. Reporting of medical device SAEs

Medical Device SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.7.

Medical Device SAE Reporting to the sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of /facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.6. Reporting of SADEs

SADE Reporting to the sponsor

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.7. Reporting of medical device deficiencies for associated person

- **Reporting to GSK**

If an Associated Person (i.e., e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter.

If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.

- Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.
- If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. Refer to Section 8.4.7 for reporting.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.6.8. Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric AEs

The DAIDS Table [DAIDS, 2017] will be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

The DAIDS table is available at the following link:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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