CLINICAL STUDY PROTOCOL

Primary study intervention(s)	GSK3228836
Other study intervention(s)	NA
Study identifier	205873
IND Number	122685
Approval date	15 Nov 2024
Title	A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers.
Compound number/Name	GSK3228836
Brief title	Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers.
Sponsor	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Dickens Theodore, MD, MPH Executive Director, Clinical Lead Clinical Research, Hepatology

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

Based on TMF-14732712 Protocol v3.0.

©2024. GSK group of companies or its licensor. Trademarks are property of their respective owners.

Protocol Amendment 2 Investigator Agreement

- 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 clinical study site agreement.
- 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 cooperate 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.

Study identifier	205873
IND Number	122685
Approval date	15 Nov 2024
Title	A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers.
Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Amendment 2	15 Nov 2024
Amendment 1	07 June 2024
Original Protocol	12 March 2024

Amendment 2 (15 Nov 2024**)**

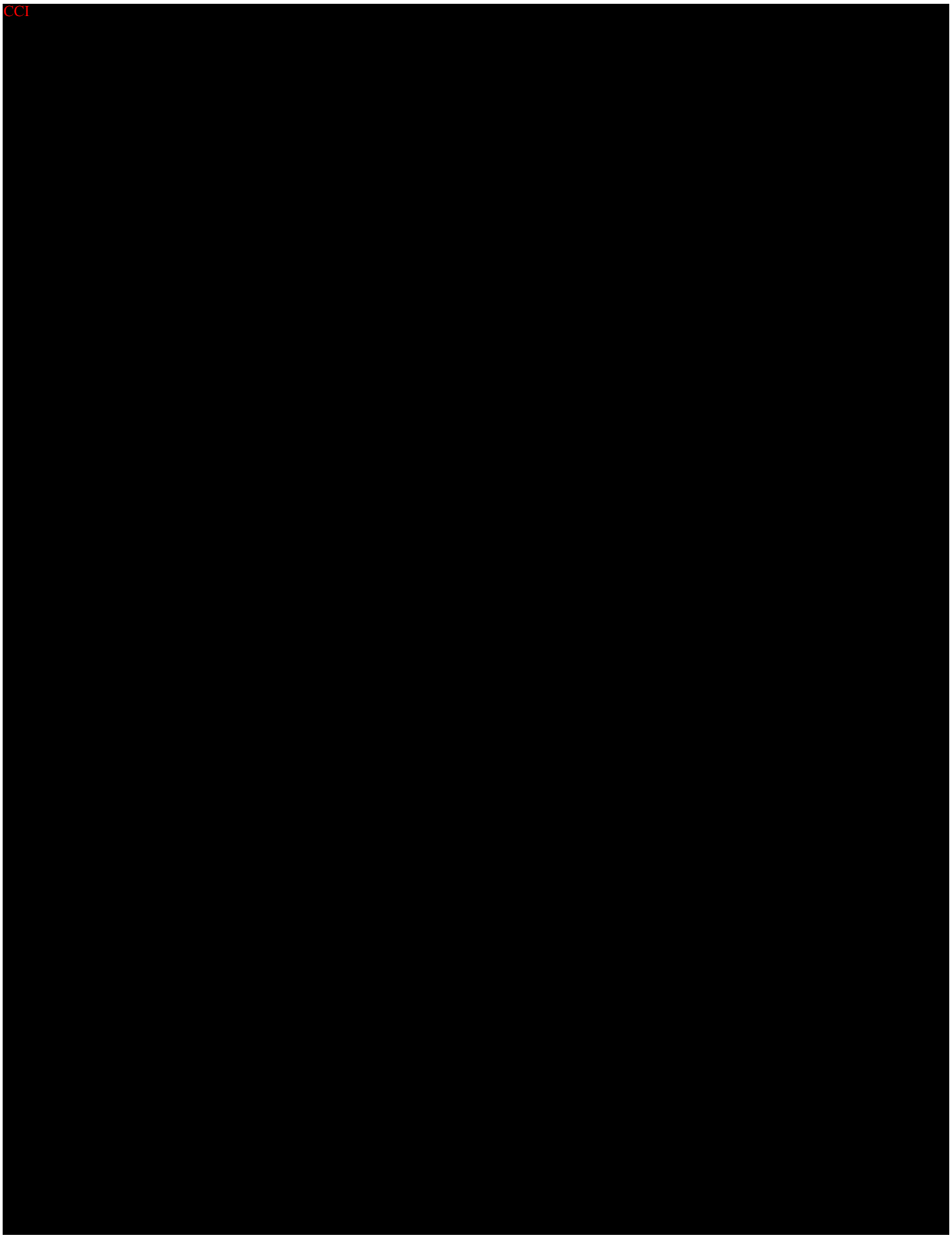
Overall rationale for the current Amendment:

The primary reason for this amendment is to reduce the dose of bepirovirsen from CCI mg to CCI mg because of tolerability issues encountered during dosing with CCI mg of bepirovirsen. Among ten participants who received either CCI mg bepirovirsen or placebo in a blinded manner, 2 participants experienced systemic adverse events and tolerated study intervention poorly. Unblinding of the 2 participants' treatment assignments confirmed that they had both received CCI mg bepirovirsen. The dose of bepirovirsen has therefore been reduced to CCI mg for the remaining 36 study participants. The dose reduction to CCI mg is supported by clinical experience from single and repeat administration of bepirovirsen in a previous phase I study (Study 213725), where the CCI mg dose was well tolerated.

Ten participants were dosed according to amendment 1. Data from these participants will be included in the final analysis, therefore some elements of amendment 1 are retained in this amendment, even though they do not apply to future participants enrolled under amendment 2.

The primary objectives, estimands, and statistical sections of the protocol have been updated with minimal modifications to accurately reflect the reduced CCI mg dose. In addition, minor typographical errors and inconsistencies have been corrected and minor editorial changes have been made.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:



CCI

[redacted]

TABLE OF CONTENTS

PAGE

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 4
List of main changes in the protocol and their rationale: 5

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 13

1. PROTOCOL SUMMARY 18
   1.1. Synopsis 18
   1.2. Schema 20
   1.3. Schedule of activities 21

2. INTRODUCTION 25
   2.1. Study rationale 25
   2.2. Background 25
   2.3. Benefit-risk assessment 26
      2.3.1. Risk assessment 26
      2.3.2. Benefit assessment 30
      2.3.3. Overall benefit-risk conclusion 30

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS 30

4. STUDY DESIGN 32
   4.1. Overall design 32
   4.2. Scientific rationale for study design 33
      4.2.1. Participant input into design 34
   4.3. Justification for dose 34
   4.4. End-of-study definition 36

5. STUDY POPULATION 37
   5.1. Inclusion criteria 37
      5.1.1. Age 37
      5.1.2. Type of participant and disease characteristics 37
      5.1.3. Weight 37
      5.1.4. Sex 37
      5.1.5. Informed consent 38
   5.2. Exclusion criteria 38
      5.2.1. Medical conditions 38
      5.2.2. Prior/concomitant therapy 39
      5.2.3. Diagnostic assessments 39
      5.2.4. Other exclusions 40
      5.2.5. Liver safety exclusion criteria 40
      5.2.6. Cardiac safety exclusion criteria 40
   5.3. Lifestyle considerations 41
      5.3.1. Meals and dietary restrictions 41
      5.3.2. Caffeine, alcohol, and tobacco 41
      5.3.3. Activity 41
      5.3.4. Other restrictions 41
   5.4. Screen failures 42
   5.5. Criteria for temporarily delaying enrollment 42

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 43
6.1. Study intervention(s) administered 43
6.2. Preparation, handling, storage, and accountability 44
6.3. Assignment to study intervention 45
6.4. Blinding, masking 45
6.5. Study intervention compliance 46
6.6. Dose modification 46
6.6.1. Retreatment criteria 46
6.7. Continued access to study intervention after the end of the study 46
6.8. Treatment of overdose 47
6.9. Prior and concomitant therapy 47
6.9.1. Rescue medicine 47

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 48
7.1. Discontinuation of study intervention 48
7.1.1. Liver event increased monitoring criteria 48
7.1.2. Drug Induced Vascular Injury and Complement Monitoring Criteria 48
7.1.3. Hematological Monitoring Criteria 49
7.1.4. Drug Induced Kidney Injury (Renal) Monitoring 49
7.1.5. QTcF stopping criteria 50
7.2. Participant discontinuation/withdrawal from the clinical study 50
7.3. Lost to follow-up 51

8. STUDY ASSESSMENTS AND PROCEDURES 52
8.1. Administrative and general/baseline procedures 52
8.1.1. Collection of demographic data 52
8.1.2. Medical history 52
8.2. Efficacy assessments 52
8.3. Safety assessments 52
8.3.1. Physical examination/history directed physical examination 53
8.3.2. Injection site reactions 53
8.3.3. Vital signs 53
8.3.4. Screening and safety ECGs 54
8.3.5. Continuous 12-Lead ECG (Holter) Monitoring 54
8.3.6. Clinical safety laboratory tests 55
8.3.7. Pregnancy testing 55
8.3.8. Study stopping / holding rules, safety monitoring AND/OR committee 56
8.4. Adverse events, serious adverse events, and other safety reporting 56
8.4.1. Time period and frequency for collecting AE, SAE, and other safety information 56
8.4.2. Method of detecting AEs and SAEs 57
8.4.3. Follow-up of AEs and SAEs 57
8.4.4. AESIs 57
8.4.4.1. ALT increases 57
8.4.4.2. Vascular Inflammation and complement activation 57
8.4.4.3. Thrombocytopenia 58
8.4.4.4. Renal Injury 58

8.4.4.5. Injection Site Reactions 58
8.4.5. Regulatory reporting requirements for SAEs 58
8.4.6. Pregnancy 59
8.4.7. CV and death events 59
8.4.8. Contact information for reporting SAEs, pregnancies and study holding rules 60
8.4.9. Participant card 60
8.5. Pharmacokinetics 60
8.6. Pharmacodynamics 61
8.7. Genetics 61
8.8. Biomarkers 61
8.9. Immunogenicity assessments 61
8.10. Health economics or medical resource utilization and health economics 61

9. STATISTICAL CONSIDERATIONS 62
9.1. Statistical hypothesis 62
9.1.1. Multiplicity Adjustment 62
9.2. Analysis sets 62
9.3. Statistical analyses 63
9.3.1. General considerations/definitions 63
9.3.2. Primary estimand analyses 63
9.3.2.1. Definition of endpoint 63
9.3.2.2. Main analytical approach 63
9.3.3. Secondary estimands analyses 65
9.3.4. Safety endpoint(s) analyses 65
9.4. Interim analyses 65
9.5. Sample size determination 66

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 67
10.1. Appendix 1: Regulatory, ethical, and study oversight considerations 67
10.1.1. Regulatory and ethical considerations 67
10.1.2. Financial disclosure 67
10.1.3. Informed consent process 68
10.1.4. Recruitment strategy 68
10.1.5. Data protection 69
10.1.6. Committees structure 69
10.1.7. Dissemination of clinical study data 70
10.1.8. Data quality assurance 70
10.1.9. Source documents 71
10.1.10. Study and site start and closure 72
10.1.11. Publication policy 73
10.2. Appendix 2: Clinical laboratory tests 73
10.2.1. Continuous Holter Monitoring 75
10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting 76
10.3.1. Definition of AE 76
10.3.2. Definition of SAE 77
10.3.3. Unsolicited AE 78
10.3.4. Definition of TEAE 78

10.3.5. Recording, assessment, and follow-up of AEs, SAEs, and pregnancies 79
10.3.5.1. AE and SAE recording 79
10.3.5.2. Assessment of intensity 79
10.3.5.3. Assessment of causality 80
10.3.5.4. Assessment of outcomes 80
10.3.5.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest 81
10.3.5.6. Updating of SAE, and pregnancy information after removal of write access to the participant's eCRF 82
10.3.5.7. Reporting of SAEs, and pregnancies 82
10.3.6. Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric AEs 83
10.4. Appendix 4: Contraceptive and barrier guidance 83
10.4.1. Definitions 83
10.4.1.1. WOCBP 83
10.4.1.2. WONCBP 83
10.4.2. Contraception guidance 84
10.5. Appendix 5: Liver safety requirements and guidelines 85
10.5.1. Liver safety: required actions, monitoring, and follow-up to assess causality of liver event 85
10.5.2. Liver safety: liver chemistry increased monitoring criteria with continued study intervention 86
10.5.3. Liver safety: study intervention restart and/or rechallenge guidelines 86
10.6. Appendix 6: Protocol Amendment History 87

11. REFERENCES 89

LIST OF TABLES

PAGE

Table 1 Screening Visit 21

Table 2 Study session, safety follow-up and early withdrawal 22

Table 3 Acceptable Visit/Time Point Windows 24

Table 4 Risk assessment 27

Table 5 Objectives and endpoints 30

Table 6 Cmax of single doses of bepirovirsen 35

Table 7 Study intervention(s) administered 43

Table 8 Study arm(s) 44

Table 9 Hematological Monitoring Criteria 49

Table 10 Timeframes for submitting SAE, pregnancy and other events reports to GSK 59

Table 11 Contact information for reporting SAEs, pregnancies and study holding rules 60

Table 12 Analysis sets 62

Table 13 Sample Size Determination - Power 66

Table 14 Protocol-required safety laboratory tests 73

Table 15 Required actions, monitoring, and follow-up to assess causality of liver event 85

LIST OF FIGURES

PAGE

Figure 1 Study design overview 20

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	Albumin to creatinine ratio
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIH	Autoimmune hepatitis
ALT	Alanine aminotransaminase
ANCA	Anti-neutrophil cytoplasmic antibodies
APTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AUC	Area Under the Concentration-time Curve
AUC (0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-24)	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose
Bb	Complement Factor Bb
BMI	Body mass index
BPM	Beats per minute
C24	Observed concentration at time 24 hours
C3/C4	Complement component 3/ Complement component 4
C5a	Complement factor C5a
c-ANCA	Cytoplasmic anti-neutrophil cytoplasmic antibodies
CFR	Code of Federal Regulations
CI	Confidence interval
Cmax	Maximum observed concentration
CONSORT	Consolidated standards of reporting trials
CPK	Creatine phosphokinase
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CTA	Clinical trials application
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DIVI	Drug Induced Vascular Inflammation
DNA	Deoxyribonucleic acid
DRC	Data review committee
DRE	Disease-related event
dsDNA	Double-stranded DNA
DSUR	Development safety update report
ECG	Electrocardiogram

Abbreviation	Definition
ED	Early discontinuation
eGFR	Estimated Glomerular Filtration Rate
EoS	End-of-study
FDA	Food and Drug Administration
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GCP	Good clinical practices
GDPR	General data protection regulation
GGT	Gamma glutanyl transferase
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HDV	Hepatitis D virus
hERG	human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HR	Heart Rate
HRT	Hormonal replacement therapy
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonization
ICSR	Individual case safety reports
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ISR	Injection site reaction
IUD	Intrauterine device
IUS	Intrauterine system
LAM	Lactational amenorrhea method
LAR	Legally authorized representative

Abbreviation	Definition
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LSLV	Last subject last visit
MCH	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume
MI	Myocardial infarction
MOE	Methoxyethyl
MPO	Myeloperoxidase
mRNA	Messenger RNA
MSDS	Material safety data sheet
Msec	Milliseconds
NOAEL	No observed adverse effect level
NQ	Non-quantifiable
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
pgRNA	Pregenomic RNA
PK	Pharmacokinetic
PP	Per Protocol
PR3	Proteinase 3
PRE	Population-related event
PT	Prothrombin Time
QTc	QT interval corrected
QTcF	Fridericia's QT correction formula
QTL	Quality tolerance limit
RAMOS	Randomization and Medication Ordering System
RBC	Red blood cell
RNA	Ribonucleic acid
RNase H	Ribonuclease H
RPGN	Rapidly progressive glomerulonephritis
RTMS	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
sC5b-9	Soluble complement 5b-9
SD	Standard Deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
siRNA	Small interfering ribonucleic acid
SoA	Schedule of activities
SPEP	Serum Protein Electrophoresis
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Definition
t½	Apparent terminal phase half-life
TEAE	Treatment-emergent adverse event
Tmax	Time of occurrence of Cmax
TOC	Table of contents
uACR	Urine albumin to creatinine ratio
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine Protein Electrophoresis
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	Definition
ADR	An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator, and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Caregiver	A "caregiver" is someone who: • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (e.g., 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.
Comparator	Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Term	Definition
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, 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.
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.
LSLV	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).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
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.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
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).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers.

Brief title: Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers.

Rationale: This study will evaluate the effect of a single supratherapeutic dose of bepirovirsen on the corrected QT interval (QTc) as compared to placebo. The ICH E14 guidance, as adopted in the US FDA Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [Department of Health and Human Services, 2005], emphasizes the need to obtain clear and robust data through studies that assess the effect of new chemical entities on ECG parameters. Specifically, the studies should evaluate a compound's effect on cardiac repolarization, as measured by the QTc. This study will be conducted to evaluate the effect of bepirovirsen on cardiac repolarization and data generated will be used to conduct concentration-QTcF analyses for bepirovirsen. ECG readings along with PK measurements will be collected to determine the relationship, if any, between bepirovirsen concentration and QT/QTcF interval prolongation. The data collected at the supratherapeutic exposure from both the CCI mg and CCI mg doses of bepirovirsen will provide confidence that the risk of the QT/QTcF interval prolongation at the therapeutic dose of 300 mg is low, along with the collected ECG measurements in the Phase 1 and 2a studies [Clinical Study Report, Study 213725, 2015][Clinical Study Report, Study 205695, 2020]. For details refer to Section 2.1 and Section 4.3.

Objectives, endpoints, and estimands:

For details refer to Section 3.

Objective(s)	Endpoint(s)
Primary	
• To determine the effect of bepirovirsen exposure (from a supratherapeutic dose) on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants estimated at Cmax using exposure-response modelling.	• Change from baseline in QTcF under bepirovirsen exposure following a supratherapeutic single dose.
Secondary	
• To evaluate the effect of bepirovirsen exposure (from a supratherapeutic dose) on other ECG parameters.	• Change from baseline in HR and QTcF, PR, and QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS) using by-time point analysis (secondary analysis). • Incidence of categorical outliers for QTcF, HR, PR and QRS. • Incidence of treatment emergent changes of T wave morphology and U-wave presence.

Objective(s)	Endpoint(s)
• To evaluate the PK of a single dose of bepirovirsen (CCI mg or CCI mg).	• Bepirovirsen plasma concentration and PK parameters (AUC(0-∞), AUC(0-24), Cmax, and Tmax).
Safety	
• To assess the safety and tolerability of a single dose of bepirovirsen (CCI mg or CCI mg) in healthy participants.	• Occurrences of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in clinical laboratory tests and vital signs.
Exploratory	
CCI [redacted]	

Overall design: This is a Phase 1, double-blind, randomized, placebo-controlled study to investigate the effect of a supratherapeutic dose of bepirovirsen on cardiac conduction, PK, safety and tolerability in healthy adult participants who will receive a single dose of bepirovirsen (CCI mg or CCI mg), or placebo on Day 1, in a 1:1 randomization. Ten participants have already been dosed with CCI mg bepirovirsen or placebo (5 active, 5 placebo). Following implementation of this protocol amendment, the remaining participants will only be dosed with bepirovirsen CCI mg or placebo on Day 1, in a 1:1 randomization.

The total duration of the study will be up to CCI (including up to 28 days of screening before Day –1). Participants will attend the clinical unit 2 days before dosing (Day –2) CCI [redacted]
CCI [redacted]

As bepirovirsen CCI mg had not been administered to humans before this study, 2 sentinel participants (1 active) were dosed initially and their safety data reviewed before dosing further participants. CCI [redacted]
CCI [redacted]
CCI [redacted]

Bepirovirsen has been previously studied at doses up to CCI mg in healthy volunteers. Therefore, no further sentinel cohort dosing will be performed for the CCI mg dose that will be administered for the remainder of the study.

For details refer to Section 4.1.

Number of participants: A total of approximately 46 participants will be enrolled and randomized to 1 of the 2 arms in a parallel design. Refer to Section 9.5. Ten participants have already been dosed, 5 of whom received CCI mg bepirovirsen. The remaining 36 participants will be randomised 1:1 in a parallel design to receive either CCI mg bepirovirsen or placebo.

Data monitoring/other committee: Refer to Section 10.1.6.

1.2. Schema

CCI



1.3. Schedule of activities

Table 1 Screening Visit

Procedure	Screening (up to 28 days before Day –1)	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.
Human immunodeficiency virus, hepatitis B and C screening	X	
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 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	
AE/SAE review	X	From signing consent.
Prior medication	X	

Table 2 Study session, safety follow-up and early withdrawal

Procedure	Day (Refer to Table 3 for allowable time windows from Day 8 onwards) CCI [redacted]										Early withdrawal	Notes
Inpatient stay	<==========X==========>											
Outpatient visit							X	X	X	X	X	
Brief physical examination	X		X[1]	X[1]		X[1]	X	X	X	X	X	[1]Within 2 h before dosing and at CCI [redacted] after dosing. Acceptable time window for CCI [redacted] is +/- 1 h. A symptom driven brief physical examination is acceptable at CCI [redacted]
Vital signs	X	X	X[2]	X[2]	X[2]	X[2]	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 2 h before dosing and at CCI [redacted] after dosing. Acceptable time window for CCI [redacted] is +/- 1 h
Drug, alcohol, and cotinine screen	X											As per standard local practice.

Procedure	Day (Refer to Table 3 for allowable time windows from Day 8 onwards) CCI										Early withdrawal	Notes
Continuous 12-lead Holter ECG recording		<==========X==========>										Continuous 12-lead ECG recording (Holter) from CCI before dosing to CCI dosing. Time of 12-lead digital ECG strip extractions (in triplicate): • On Day -1, ECG strips will be extracted from the continuous ECG recording at the following time points (relative to the time of planned dosing on Day 1): CCI • Before dosing on Day 1, ECG strips will be extracted from the continuous ECG recording at CCI CCI prior to dosing. After dosing on Day 1, ECG strips will be extracted from the continuous ECG recording at CCI CCI Further details in Section 8.3.5.
Safety 12-lead ECG	X		X[3]	X[3]	X[3]	X[3]	X	X	X	X	X	All safety ECGs to be performed in triplicate. [3]Within 2 h before dosing and at CCI after dosing. Acceptable time window for CCI is +/- 1 h. Details on QTc safety monitoring are available in Section 7.1.5.
Pregnancy test		X[4]								X	X	Serum or urine. WOCBP only. [4]Within 24 h before dosing.
Clinical chemistry and hematology	X		X[5]	X[5]		X[5]	X	X	X	X	X	[5]Within 2 h before and at CCI after dosing. Acceptable time window for CCI is +/- 1 h.
Urinalysis	X		X[6]	X[6]		X[6]	X	X	X	X	X	[6]Within 5 h before and at CCI after dosing. Acceptable time window for CCI is +/- 1 h.
Urine ACR			X[7]	X[7]		X[7]		X		X	X	[7]Within 5 h before and at CCI after dosing. Acceptable time window for CCI is +/- 1 h.
C3, C4, p-ANCA, c-ANCA			X								X	Within 2 h before dosing. Post-dose samples should be collected, at the discretion of the PI, if there is suspected vascular inflammation.
hs-CRP			X[8]	X[8]		X[8]		X	X	X	X	[8]Within 2 h before dosing and at CCI after dosing. Acceptable time window for CCI is +/- 1 h.

Procedure	Day (Refer to Table 3 for allowable time windows from Day 8 onwards)										Early withdrawal	Notes
	–2	–1	1	2	3	4	8	15	29	50		
Coagulation Panel (PT, INR, APTT)			X[9]	X[9]		X[9]	X	X	X	X	X	[9]Within 2 h before and at CCI after dosing. Acceptable time window for CCI is +/- 1 h
Randomization		X										At any time on Day –1 or before dosing on Day 1.
Single dose of bepirovirsen or placebo			X									
CCI												
Assessment of injection site			X[12]	X[12]	X[12]	X[12]	X	X	X	X	X	[12]Within 2 h before dosing and at CCI after dosing. Acceptable time window for CCI is +/- 1 h.
AE review	<==========X==========											
SAE review	<==========X==========											
Prior/ concomitant medication review	<==========X==========											

Table 3 Acceptable Visit/Time Point Windows

Assessment	Planned Timepoint	Acceptable window
Safety and Laboratory assessments*	CCI	

*Brief physical examination, Vital signs, safety ECG, clinical laboratory tests, assessment of injection site.

2. INTRODUCTION

2.1. Study rationale

This study will evaluate the effect of a single dose of bepirovirsen on the corrected QT interval (QTc) as compared to placebo. The ICH E14 guidance, as adopted in the US FDA Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [Department of Health and Human Services, 2005], emphasizes the need to obtain clear and robust data through studies that assess the effect of new chemical entities on ECG parameters. Specifically, the studies should evaluate a compound's effect on cardiac repolarization, as measured by the QTc. This study will be conducted to evaluate the effect of bepirovirsen on cardiac repolarization and data generated will be used to conduct concentration-QTcF analyses for bepirovirsen. ECG readings along with PK measurements will be collected to determine the relationship, if any, between bepirovirsen concentration and QT/QTcF interval prolongation. The exposure data collected from supratherapeutic single doses of bepirovirsen will be used to provide confidence that the risk of QT/QTcF interval prolongation at the therapeutic dose of 300 mg is low, along with the collected ECG measurements in the Phase 1 and 2a studies [Clinical Study Report, Study 213725, 2015][Clinical Study Report, Study 205695, 2020].

A supratherapeutic dose is defined as a dose that provides exposures (mean Cmax) exceeding the high clinical scenario [ICH E14/S7B Questions and Answers 5.1, 2022]. A full description of the liquid drug product is given in the IB [GSK Document Number RPS-CLIN-047928].

2.2. Background

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, 2021]. Bepirovirsen allows resumption of a host immune response against HBV and infected cells and can induce HBsAg seroclearance. CCI [redacted] [Clinical Study Report, Study V72411G, 2022].

At the time of this protocol submission, GSK has completed 2 Phase 2b studies in participants with chronic HBV that have shown low incidence of cardiac safety risk or ECG abnormalities. Summaries of the preclinical and clinical studies are included in the IB [GSK Document Number RPS-CLIN-047928].

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.

2.3.1. Risk assessment

Relevant risks associated with bepirovirsen treatment in this study are summarized in Table 4.

Additional monitoring for liver chemistry, DIVI, platelet count, and renal function are discussed in Section 7.1.

The supratherapeutic dose of CCI mg had not been studied before enrolment in this study began, and the risks associated with this dose were not known. Review of the blinded safety data from CCI (4 active) subsequently dosed in this study, suggested that systemic AEs may be more frequent and/or more severe in participants randomised to CCI mg bepirovirsen or placebo compared to previous studies that used CCI of bepirovirsen. Two of the 10 randomized participants exhibited a variety of symptoms of mild and moderate severity, including headache, nausea, vomiting, myalgia, and dizziness. These symptoms were associated with low-grade fever and/or elevated CRP, suggestive of a systemic inflammatory response. These participants experienced discomfort for up to 48 hours after dosing, despite symptomatic treatment. Unblinding of these 2 participants confirmed that both of them had received CCI mg bepirovirsen.

A total of 6 healthy participants have previously received CCI mg bepirovirsen in single or multiple dose studies. The frequency and type of AEs associated with this dose do not appear to differ meaningfully from those observed with the 300 mg therapeutic dose.

Based on a review of the available data, administration of a single dose of bepirovirsen minimizes the potential risks associated with bepirovirsen treatment, and the CCI mg dose is anticipated to be more tolerable than the CCI mg dose.

Table 4 Risk assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Study intervention(s) bepirovirsen		
Non-clinical risks		
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 7.1.2).
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'-MOE ASOs. Review of the 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 to 1.5×ULN in 1 participant treated with 300 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 chronic HBV in which bepirovirsen was given weekly for 4 weeks and 24 weeks, respectively, and where ALT increases >3×ULN were observed, showed no evidence of	Hepatic enzyme monitoring will be performed (see Section 7.1.1).

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	DILI. The likelihood is that ALT increases are an indication of therapeutic effect.	
Thrombocytopenia leading to clinically significant bleeding events	Two types of thrombocytopenia have been described for the 2'-methoxyethyl ASOs [Chi, 2017; Crooke, 2017]: • rapid onset, unpredictable thrombocytopenia. • gradual decline in platelets leading to mild to severe thrombocytopenia, can be asymptomatic or associated with mild to severe bleeding (more common). In monkeys given bepirovirsen (39 week study), there were incidences of both types of thrombocytopenia [GSK Document Number 2019N419364, 2015]. Thrombocytopenia was not reported in the Phase 1 (Study 213725) [Clinical Study Report, Study 213725, 2015] or Phase 2a (Study 205695) [Clinical Study Report, Study 205695, 2020] clinical studies. In the Phase 2b studies (209668 [Clinical Study Report, Study 209668, 2023] and 209348 [Clinical Study Report, Study 209348, 2023]), platelet count did decline to below 100×10^9/L. Clinically significant bleeding events were not reported.	Monitoring of platelet count will be performed with direction to the investigator on what action to take depending on platelet count (Section 7.1.3).
Drug-Induced Kidney Injury (DIKI)	Glomerulonephritis has been reported with ASOs and is thought to be a result of the proinflammatory effect of ASOs. No AEs related to renal function were reported in the Phase 2a study (Study 205695) [Clinical Study Report, Study 205695, 2020] Fluctuation in eGFR were seen in Phase 2b studies (209668 [Clinical Study Report, Study 209668, 2023] and 209348 [Clinical Study Report, Study 209348, 2023]) but no associated changes in other renal laboratory parameters or urinalysis have been identified. The available data do not suggest that bepirovirsen is associated with renal injury.	Monitoring of renal laboratory parameters will be performed with direction to the investigator on what action to take depending on renal laboratory criteria (Section 7.1.4).

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
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 pain, injection site erythema and injection site pruritis. Few events have led to treatment discontinuation.	Participants will be assessed for ISRs at all visits as per the SoA. All [redacted] injections should be administered at different injection sites at least 5cm apart to minimize ISR. Further details in Section 6.1.
Study procedures		
Blood draws	Risks with phlebotomy include bruising, bleeding, infection and nerve damage.	Procedures to be performed by trained personnel.

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 bepirovirsen for patients with chronic HBV.

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

Table 5 Objectives and endpoints

Objective(s)	Endpoint(s)
Primary	
• To determine the effect of bepirovirsen exposure (from a supratherapeutic dose) on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants estimated at Cmax using exposure-response modelling.	• Change from baseline in QTcF under bepirovirsen exposure following a supratherapeutic single dose.
Secondary	
• To evaluate the effect of bepirovirsen exposure (from a supratherapeutic dose) on other ECG parameters.	• Change from baseline in HR and QTcF, PR, and QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS) using by-time point analysis (secondary analysis). • Incidence of categorical outliers for QTcF, HR, PR and QRS. • Incidence of treatment emergent changes of T wave morphology and U-wave presence.
• To evaluate the PK of a single dose of bepirovirsen (CCI mg or CCI mg).	• Bepirovirsen plasma concentration and PK parameters (AUC(0-∞), AUC(0-24), Cmax, and Tmax).
Safety	
• To assess the safety and tolerability of a single dose of bepirovirsen (CCI mg or CCI mg) in healthy participants.	• Occurrences of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in clinical laboratory tests and vital signs.
Exploratory	
CCI	

PRIMARY ESTIMAND

The primary question of interest is: Is there a clinically significant and clinically relevant effect of bepirovirsen exposure, following a supratherapeutic dose, on cardiac conduction as measured by a change in QTcF from baseline.

The estimand is described by the following attributes:

- Population: Healthy participants.
- Treatment: A single dose of bepirovirsen (either CCI or CCI mg) or matching placebo.
- Variable/endpoint: Change in QTcF from baseline (ΔQTcF).
- Summary measure: Geometric mean and 90% confidence interval of ΔΔQTcF (placebo-corrected change from baseline) predicted from a concentration-QT model at the mean Cmax following a supratherapeutic single dose of CCI mg.
- Intercurrent events: Any event leads to a non-full dose – Treatment Policy strategy will be applied to address this intercurrent event.
- Rationale for estimand: Interest lies in the overall relationship between the ΔQTcF and bepirovirsen concentrations while the participant is exposed to bepirovirsen. Therefore, even though the concentration for a dose is affected, the data are still relevant.

SECONDARY ESTIMANDS

Secondary estimands address the clinical question in (1) Effect of bepirovirsen on other ECG parameters at concentrations following a supratherapeutic dose, as measured by placebo-corrected changes from baseline in HR, QTcF, PR, QRS; and (2) PK of a single dose bepirovirsen (CCI or CCI mg). The endpoints for the secondary objectives will be summarized by dose.

The estimand is described by the following attributes:

- Population: Healthy participants.
- Treatment: a single dose of bepirovirsen (either CCI or CCI mg) or matching placebo.
- Variable/endpoint:
  1) Change from baseline in HR and QTcF, PR and QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS) using by-time point analysis.
  2) Incidence of outliers for QTcF, HR, PR, and QRS.
  3) Incidence of treatment-emergent changes of T wave morphology and U-wave presence.
  4) Plasma concentration of bepirovirsen.
- Summary measure:
  1) Placebo corrected change from baseline in HR, PR, QTcF, and QRS (ΔΔHR, ΔΔPR, and ΔΔQRS) using by timepoint analysis.
  2) Frequency counts and percentage of categorical outliers for QTcF, HR, PR, and QRS by events and participants.

3) Frequency counts and percentage of treatment emergent changes of T wave morphology and U-wave presence by participants and events.

4) Descriptive summary statistics of plasma concentration of bepirovirsen.

5) Descriptive summary of plasma PK parameters of bepirovirsen: geometric mean and geometric %CV will be calculated for AUC(0-24), AUC(0-∞), Cmax and median and range for Tmax.

- Intercurrent events: Any event leads to a non-full dose – Principal stratum strategy will be applied to address this intercurrent event.
- Rationale for estimand: Interest lies in the effect on ECG parameters and plasma PK using by timepoint analysis following a single dose of bepirovirsen (CCI or CCI mg). A non-full dose will dampen the ECG effect and PK.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 1, double-blind, randomized, placebo-controlled study to investigate the effect of a supratherapeutic dose of bepirovirsen on cardiac conduction, PK, safety, and tolerability in healthy adult participants.

A total of approximately 46 participants will be enrolled and randomized 1:1 into parallel arms to receive a single supratherapeutic dose of bepirovirsen, CCI mg (prior to protocol amendment 2) or CCI mg (protocol amendment 2 onwards), or matching placebo. Doses will be administered as subcutaneous injections of bepirovirsen CCI mg or placebo at a single time point. PK and ECG collection will be identical for both arms (see Section 4.3).

Since the bepirovirsen CCI mg dose had not been previously administered to humans, this study was designed to include a sentinel cohort of 2 participants (1 active CCI mg bepirovirsen, 1 placebo). At least 7 days after dosing, and before further participants could be randomized, a meeting occurred between the Principal Investigator and sponsor medical monitor to review blinded sentinel cohort safety and tolerability data up to Day 4. The data reviewed included AEs/SAEs, laboratory results, safety 12-lead ECGs, and vital signs.

CCI [redacted]
CCI [redacted] At least 7 days after the participants were dosed, and before dosing further study participants, the GSK SRT reviewed blinded safety and tolerability data (including AE/SAEs, laboratory results, safety 12-lead ECGs, and vital signs) up to CCI [redacted] in the second cohort, as well as all available safety data from the 2 sentinel participants. Among the CCI participants dosed, 2 experienced tolerability issues related to systemic AEs (Section 2.3). A decision was made not to dose any further participants with bepirovirsen CCI mg due to the tolerability concerns, and to reduce the bepirovirsen dose to CCI mg for all subsequent participants.

Unblinding the treatment assignment of the 2 participants who had experienced tolerability issues related to systemic AEs revealed that both participants had received the CCI mg bepirovirsen dose.

The remaining 36 participants in the study will be randomised to receive either CCI mg bepirovirsen or placebo, in a 1:1 randomization. As clinical experience has been gained with the CCI mg dose in previous studies, there will be no sentinel participant dosing following reduction of the dose to CCI mg.

Participants will be screened within 28 days before Day –1 (the day before dosing). They will attend the clinical unit 2 days before dosing (Day –2) and will remain inpatient until CCI. Going forward, from protocol amendment 2, they will receive a single dose of bepirovirsen CCI mg or placebo on Day 1.

Participants will return for outpatient visits CCI days after dosing (CCI CCI). The total duration of study participation including screening for each participant will be up to CCI

Blood samples will be taken to measure levels of bepirovirsen before dosing and until CCI after dosing. Time-matched ECG recordings will be taken at all PK sampling time points, as described in Section 8.3.5 and Section 8.5. Safety and tolerability will be assessed from before dosing until the final visit.

The study design schematic is presented in Figure 1.

4.2. Scientific rationale for study design

The design of this study includes 2 groups: a single supratherapeutic bepirovirsen dose or matching placebo in parallel arms. Prior to protocol amendment 2, bepirovirsen doses of CCI mg or placebo were administered as [redacted] subcutaneous injections at a single time point; in all subsequent dosing, bepirovirsen doses of CCI mg or placebo will be administered as [redacted] subcutaneous injections at a single time point. PK and ECG collection will be identical for both arms.

CCI
CCI
CCI [ICH E14/S7B Questions and Answers 5.1, 2022]. As tolerability concerns have prevented further dosing with CCI mg, the supratherapeutic dose has been reduced to CCI mg. Based on observations from a previous study, the reduced dose of CCI mg will provide exposures CCI than the high clinical exposure scenario. The combined data from both the CCI mg and CCI mg doses will be utilized for model development, allowing for characterization of the QT interval at a sufficient margin above the high clinical exposure scenario. It is important to note that bepirovirsen exposures from the 300 mg weekly therapeutic dose are considered representative of the highest clinical exposure scenario since bepirovirsen exposures are not expected to be increased due to drug-drug interactions or upon dosing in patients with organ impairment. A nonclinical integrated

risk assessment, as per ICH E14-S7B guidelines, has also been provided previously as supplementary evidence [ICH E14/S7B Questions and Answers 5.1, 2022].

For the initial CCI mg dose, sentinel participants (1 active, 1 placebo) were dosed at least 7 days before dosing the next cohort. As clinical experience has been gained with the CCI mg dose in previous studies, there will be no sentinel participants in the study following reduction of the dose to CCI mg.

4.2.1. Participant input into design

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

4.3. Justification for dose

Prior to this study, bepirovirsen has been studied in doses up to CCI mg (both single and multiple dose) in Phase 1 studies. The therapeutic dose of bepirovirsen is 300 mg administered CCI , with loading doses at CCI . For the purposes of a QTcF study, CCI CCI CCI . A supratherapeutic dose is defined as a dose that provides exposures exceeding the high clinical exposure scenario [ICH E14/S7B Questions and Answers 5.1, 2022]. Exposures of bepirovirsen were simulated at various dose levels using a previously developed population PK model [Population Pharmacokinetic Analyses for Bepirovirsen , 2023]; these exposures were compared to those achieved by the therapeutic dose of 300 mg. Based on its ADME profile and consistent with other oligonucleotides, bepirovirsen has CCI as well as low potential to be impacted by changes in renal or hepatic function (Bepirovirsen IB [GSK Document Number RPS-CLIN-047928]); as such, the exposures achieved with the 300 mg weekly dose are considered to represent the highest clinical exposure scenario. A supratherapeutic dose of CCI mg was originally chosen to assess potential for QT prolongation, supported by results of population PK model-based simulations.

The administration of a single dose of bepirovirsen at CCI mg was expected to provide exposures CCI of the expected clinical exposure achieved with the 300 mg therapeutic dose. CCI CCI CCI CCI CCI

Given the AEs due to tolerability observed in 2 participants who received the CCI mg bepirovirsen dose out of 10 dosed participants, the decision was made to unblind the PK data for those 2 participants and compare this against summary PK data in the other participants who received bepirovirsen. The mean and SD of the Cmax for the CCI mg dose was CCI CCI . The Cmax from the 2 participants who experienced

tolerability issues were CCI When reviewing the observed exposures from the highest previously administered dose of bepirovirsen at CCI mg [Clinical Study Report, Study 213725, 2015], the mean Cmax at Day 1 including both the single-ascending dose and multiple-ascending dose cohorts was CCI CCI than the mean Cmax achieved with the therapeutic dose of 300 mg CCI. Based on these observations, and the acceptable safety and tolerability profile of the CCI mg dose as observed in a previous clinical study, the decision was made to reduce the administered dose in this current study to CCI mg, which still achieves supratherapeutic exposures as compared to the therapeutic dose, which delivers the high clinical exposure scenario.

Due to the lack of DDI potential and low potential to be impacted by organ impairment, the CCI mg dose enables the assessment of effects on the QT interval at exposures exceeding those of the high clinical exposure scenario (Table 6) with a lower risk of tolerability issues, based on existing clinical data. Additionally, the primary analysis will include data from participants in both the CCI mg and CCI mg cohorts, as this data were collected in a double-blind manner and represents objective measures. The inclusion of exposure and QT data from both the CCI mg and CCI mg doses will maximize the range of data to be included in the analysis and allow for a characterization of the QT interval at exposures higher than those expected with the high clinical exposure scenario.

CCI

The administration of a single dose of CCI mg or CCI mg bepirovirsen within the context of this study is supported by the GLP nonclinical safety package, as outlined in the Bepirovirsen IB [GSK Document Number RPS-CLIN-047928]. Bepirovirsen had CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

In the monkey 13-week repeat dose toxicology study the NOAEL was defined as CCI which affords a margin of CCI the predicted Cmax and AUC, respectively, at CCI mg or CCI mg in human. CCI CCI CCI No other adverse clinical observations or clinical pathology and histopathology changes were noted in any other animal in this study, including those treated at CCI CCI. Critically, the adverse platelet effects were not noted in the affected animal until CCI onwards. Additionally, monkeys were dosed on 4 occasions in the first week of the study (Days 1, 3, 5 and 7), followed by weekly dosing, thereafter, as opposed to the single dose planned in this study. Given that platelet levels are monitorable and decreases only manifest with repeat dosing of bepirovirsen (and shown to be reversible in the monkey and human), it is considered that the CCI dose group is relevant for defining margins for this single dose study. Thus, based on Day 1 toxicokinetic data, the CCI dose level affords a margin of CCI the predicted Cmax and AUC, respectively, at CCI mg or CCI mg in human.

In the prior single dose study in healthy volunteers that had a maximum dose of CCI mg [Clinical Study Report, Study 213725, 2015], most adverse reactions were related to injection site reactions. Transient increases in CRP were the second most common finding in the study and were not associated with clinical symptoms. This has been observed with other 2'MOE ASOs [Flaim, 2014]. An ALT increase of <2 × ULN was observed in 1 participant at 300 mg in the single dose study. Participants (n=3) dosed with a single dose of CCI mg bepirovirsen had ALT < ULN. ALT increases were not associated with bilirubin increases and were without clinical symptoms. Other changes in laboratory results included modest prolongation of APTT that was not clinically significant, has been observed with other 2'MOE ASOs and resolved within 12 to 24 hours post dose. Post baseline increases in CPK to >ULN were observed after single dose administration and were not associated with adverse effects.

Considering the administration of bepirovirsen as a subcutaneous injection and volume limitations per injection, both CCI mg and CCI mg provide an adequate exposure margin while also allowing for practical dose administration.

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 EoS 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:

5.1.1. Age

- Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent. INC#1

5.1.2. Type of participant and disease characteristics

- Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, ECGs and vital signs. INC#2

5.1.3. Weight

- Body weight ≥50 kg and BMI within the range 19–32 kg/m^2 (inclusive). INC#3

5.1.4. Sex

- Male Participants: There are no contraceptive requirements for male participants. INC#4

- Female Participants: INC#5

- 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 Section 10.4.

  OR

  - is a WOCBP and using a contraceptive method (for at least 28 days prior to enrolment [first dose of study drug]) that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4, during the intervention period and for at least 7 days after the last dose of study treatment 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 treatment.

- 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.

- Additional requirements for pregnancy testing during and after the study intervention are located in Section 8.3.5.

- 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.

5.1.5. Informed consent

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. INC#6

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- 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. EXC#1
- History of vasculitis or presence of symptoms and signs of potential vasculitis (e.g., vasculitic rash, skin ulceration, repeated blood detected in urine without identified cause), current or history of an autoimmune condition or history/presence of other diseases that may be associated with vasculitis condition (e.g., systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, mononeuritis multiplex). EXC#2
- A sustained supine systolic blood pressure >150 mm Hg or <90 mm Hg or a supine diastolic blood pressure >95 mm Hg or <50 mm Hg at Screening or Check-in (Day-2). Blood pressure may be retested once in the supine position. The blood pressure abnormality is considered sustained if either the systolic or the diastolic pressure values are outside the stated limits after 2 assessments, in which case the participant may not be randomized. EXC#3
- A supine mean heart rate outside the range 50 to 100 bpm. A HR from 100 to 110 bpm can be rechecked, using the mean HR from the screening ECGs or by repeat vital signs, within 2 hours, to verify eligibility. EXC#4

- Lymphoma, leukemia, or any malignancy except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years. EXC#5
- Participants with any other medical conditions which, in the judgement of the investigator and/or Medical Monitor, could jeopardize the integrity of the data derived from that participant or the safety of the participant. EXC#6
- Platelets $<140 \times 10^9$/L. EXC#7
- Serum calcium, magnesium or potassium levels outside the normal reference range at screening. EXC #8

5.2.2. Prior/concomitant therapy

- 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 the protocol Section 6.9 may be allowed. EXC#9
- Current or prior use of creatine-containing supplements or intended use up to 50 days post-dosing. EXC#10
- Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months before dosing. EXC#11
- Loss of blood or blood products in excess of 500 mL within a 3-month period. EXC#12
- Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. EXC#13
- 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 signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research. EXC#14
- Current enrollment or past participation in this clinical study. EXC#15

5.2.3. Diagnostic assessments

- Positive pre-clinical drug/alcohol screen, including Tetrahydrocannabinol (tetrahydrocannabinol). EXC#16
- Positive HIV antibody test. EXC#17
- Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening. EXC#18

5.2.4. Other exclusions

- Regular alcohol consumption within 6 months prior to screening 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. EXC#19
- Regular use of known drugs of abuse, including tetrahydrocannabinol. EXC#20
- Sensitivity to heparin or history of heparin-induced thrombocytopenia. EXC#21
- 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. EXC#22

5.2.5. Liver safety exclusion criteria

- ALT >1.5×ULN. EXC#23
- Total bilirubin >1.5×ULN; Participants with Gilbert's syndrome can be included with total bilirubin >1.5×ULN as long as direct bilirubin is ≤1.5×ULN. EXC#24
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). EXC#25
- Presence of HBsAg at screening or within 3 months prior to first dose of study intervention. EXC#26
- Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. EXC#27

  Note: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
- Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. EXC#28

  Note: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

5.2.6. Cardiac safety exclusion criteria

- Known history of heart disease, including ischemic heart disease, cardiomyopathy, clinically significant cardiac arrhythmias, clinically significant valvular disease, or hypertensive heart disease. EXC#29
  a. History of palpitations associated with presyncope or syncope, or history of unexplained syncope.
  b. History of Brugada syndrome, ventricular pre-excitation syndromes, personal or family history of long QT syndrome, or family history of sudden cardiac death.
- Exclusion criteria for Screening ECG: EXC#30
  a. QTcF >450 msec[1].

b. QRS interval >120 ms

c. PR interval >210 ms

d. An uninterpretable ECG or any significant arrhythmia or conduction abnormality which, in the opinion of the investigator or GSK Medical Monitor, will interfere with the safety of the individual participant.

Notes:

[1]The QTcF is the QT interval corrected for heart rate according to Fridericia's formula, machine read or manually over-read.

The method used to determine eligibility and discontinuation for an individual participant should be consistent and determined before initiation of the study.

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice (pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 7 days before the start of study intervention until after collection of the final PK sample.

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 24 hours before the dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
- Participants who use tobacco products will be instructed that use of tobacco and nicotine-containing products (including nicotine patches) will not be 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 72 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

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 SAE.

Individuals who do not meet the criteria for participation in this study based on 1 out of range test result, may be retested once.

Individuals who meet the eligibility criteria but fall out of the screening window, may be rescreened at the discretion of the investigator and Medical Monitor.

Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' eCRF.

5.5. Criteria for temporarily delaying enrollment.

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Table 7 Study intervention(s) administered

Intervention label	Bepirovirsen	Placebo
Intervention name	Bepirovirsen, (GSK3228836)	Placebo
Intervention description	Clear colorless to yellow solution	Clear colorless solution
Type	Drug	Drug
Dose formulation	Solution for injection	Solution for injection
Unit dose strength(s)	CCI nominal volume per vial (minimal overfill per vial)	Vial: Locally sourced normal saline
Dosage level(s)	Sentinel cohort and second cohort: CCI mg once. CCI CCI CCI mg dose. All other cohorts: CCI mg once. CCI injections required to deliver CCI mg dose.	Sentinel cohort and second cohort: CCI injections required to deliver placebo All other cohorts: CCI injections required to deliver placebo
Route of administration	SC Injection	SC Injection
Use	IMP	Placebo
Sourcing	Provided centrally by the sponsor	Locally sourced normal saline.
Packaging and labelling	Study intervention will be provided in vials. Each vial will be labelled as required per country requirement.	Study intervention will be provided in container. Each container will be labelled as required per country requirement.

Bepirovirsen Solution for Injection, CCI, is a clear, colorless to yellow solution, essentially free from visible particles. Bepirovirsen vial is presented as a 1 mL nominal fill volume of Bepirovirsen Solution for Injection CCI in a 3 mL clear glass vial, closed with a chlorobutyl 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 or CCI mg. It is recommended to use 27G thin-wall needles or 25G regular-walled needles for injection.

Anatomic areas for injection are listed in order of preference and are a guide for the clinical staff.

1. Abdominal quadrants
2. Thighs
3. Upper outer arms

Each injection should be given at a different site, at least 5 cm from a previous injection site. No more than 2 injections should be administered per thigh or abdomen quadrant, and no more than 1 injection per upper outer arm.

Injection into skin lesions, areas of bruising or inflammation, or sites used for recent injectable medicine administration (e.g. vaccines) should be avoided.

Table 8 Study arm(s)

Arm title	Bepirovirsen	Placebo
Arm type	experimental	placebo
Arm description	Participants will receive CCI × 150 mg/mL injections subcutaneously for a total single dose of CCI or CCI mg on Day 1.	Participants will receive CCI × 1 mL injections subcutaneously on Day 1.
Associated intervention labels	Bepirovirsen	Placebo

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 may supply, prepare, or administer study intervention.
- 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 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

Type of study	
Study using RTMS	All participants will be centrally assigned to randomized study intervention using an RTMS and computer generated randomization schedule by the sponsor. Once a randomization number has been assigned, it must not be re-assigned Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

6.4. Blinding, masking

Blinded study with unblinded third party (pharmacist/study nurse/site staff) who is dispensing intervention.

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavour to ensure that there are no differences in time taken to dispense following randomization.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.

Investigators and site staff could infer treatment assignment due to:

- Differences in the injection force due to the viscosity of bepirovirsen versus placebo saline.
  - This is minimized by the use of 27G thin-walled needles or 25G regular-walled needles.
- Color difference of bepirovirsen versus placebo saline
  - Syringes will be wrapped in a colored transparent tape to prevent unblinding of the participant and blinded site staff.

Emergency Unblinding

This is a double-blind study in which participants/ care providers/ investigators/ outcomes assessors, etc. are blinded to study intervention. The RAMOS system used for unblinding will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact

GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If the investigator is unable to access RAMOS, they can contact the GSK Clinical Support Helpdesk based on the information provided in the pharmacy manual.

A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

A participant may continue in the study if that participant's intervention assignment is unblinded.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited safety report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

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, 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 single dose study in which dose modification is not permitted.

6.6.1. Retreatment criteria

All participants entered into the study will be treated at Day 1. This is a single dose study in which there is no retreatment.

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 the planned dose for the cohort (i.e. sentinel cohort and second cohort: CCI mg, and the remaining participants: CCI 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 should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted.
- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 50 days), or as medically appropriate.
- Obtain a plasma sample for PK analysis immediately and through 7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

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.

Paracetamol/Acetaminophen, at doses of ≤2 g/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.

6.9.1. Rescue medicine

Not applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable.

Monitoring criteria are outlined in the section below.

7.1.1. Liver event increased monitoring criteria

Liver event increased monitoring criteria and required actions and follow-up assessments have been designed to assure participant safety and evaluate liver event etiology.

If the following criteria are met, increased liver chemistry monitoring and follow-up assessments are required:

- ALT ≥3×ULN.
- ALT ≥3×ULN AND bilirubin ≥2×ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2×ULN, and direct bilirubin ≥2×ULN and at least doubled from baseline value) or ALT ≥3×ULN and INR >1.5.
  - If possible Hy's Law case: ALT ≥3×ULN and total bilirubin ≥ 2×ULN (>35% direct) or INR >1.5, report as an SAE.

Refer to Section 10.5.1 for required liver safety actions, monitoring and follow-up to assess causality of liver event.

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 5 should be instituted if defined parameters are reached.

7.1.2. Drug Induced Vascular Injury and Complement Monitoring Criteria

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, vasculitic/purpuric rash, signs of renal involvement, for example (hematuria; increasing presence of blood on urine microscopy, increasing urine ACR, rising creatinine, falling GFR), jaundice, hemolysis 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).

7.1.3. Hematological Monitoring Criteria

If a participant's platelet count is $<100\times10^9$/L, bepirovirsen should not be administered. Platelet counts must be re-checked as soon as possible (with a new blood sample) if the platelet count is uninterpretable, below LLN reference range for healthy participants, or the sample shows platelet clumping.

Participants with platelet counts $<75\times10^9$/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.

Monitoring criteria are shown in Table 9.

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

Table 9 Hematological Monitoring Criteria

Platelet Count Value	Monitoring
75 × 10^9/L ≤ platelets <100 × 10^9/L	Monitor per SoA or at least weekly until ≥100 × 10^9/L
50 × 10^9/L ≤ platelets <75 × 10^9/L	Assess anti-platelet antibodies. Monitor every 2 to 3 days until 3 successive measurements ≥75 x 10^9/L, then weekly until ≥100 × 10^9/L.
<50 × 10^9/L	Assess anti-platelet antibodies. Monitor daily until >25 × 10^9/L, then every 2 to 3 days until 3 successive measurements ≥75 × 10^9/L, then weekly until ≥100 × 10^9/L.

7.1.4. Drug Induced Kidney Injury (Renal) Monitoring

If any of the following are observed, results should be confirmed (with a new specimen), 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 per SoA (Section 1.3). If after Day 15, monitor at least 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], treatment for RPGN should be initiated promptly.

7.1.5. QTcF stopping criteria

As this is a single dose study, there are no QTcF stopping criteria.

The same method of determining QTcF (machine or manual over-read) must be used for each individual participant to determine eligibility and for safety monitoring.

If a participant develops an on-treatment QTcF >500 msec or an increase from baseline QTcF >60 msec (based on the average of the triplicate safety ECGs), then the participant should have the following:

1) A complete unscheduled chemistry panel;
2) An unscheduled PK sample; and

Repeated unscheduled triplicate safety ECGs with time-matched unscheduled PK samples according to the Investigator's clinical discretion until the participant's QTcF measurement is <450 msec (based on the average of triplicate ECGs).

7.2. Participant discontinuation/withdrawal from the clinical 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 withdrawing from the study, if possible, an ED visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and possible follow-up 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 available for 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 withdrawal from the study will be documented in the 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 until the event is resolved (see Section 10.3.5.5).

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/other contact methods, 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. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of "screen failure."
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year 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

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to study start in the eCRF.

8.2. Efficacy assessments

Not applicable.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA. 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 (CV, skin, respiratory, gastrointestinal, and neurological) systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the (skin, lungs, CV system, and abdomen [liver and spleen]).
- 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 3).

8.3.3. Vital signs

- Temperature, heart rate, respiratory rate and blood pressure will be assessed as outlined in the SoA (before blood collection for laboratory tests) (Section 1.3).
- Blood pressure and heart rate measurements will be assessed in a supine or semi-supine position. Supine vital signs are required at screening and when vital sign measurement coincides with a supine rest period (Section 8.3.5). A completely automated device will be used and manual techniques 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 blood pressure measurements during screening and before dosing, 3 consecutive blood pressure 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 blood pressure readings will be recorded in the eCRF.
- Vital signs should be taken before blood collection for laboratory tests.

8.3.4. Screening and safety ECGs

- 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- At each timepoint where triplicate safety ECGs are required, 3 separate ECGs will be performed consecutively at intervals of approximately 1 minute. The full set of triplicates should be completed within a 5 minute period. The average electrocardiographic values across the 3 ECGs will be recorded.

8.3.5. Continuous 12-Lead ECG (Holter) Monitoring

Continuous 12-lead ECG recordings will be carried out from Day -1, approximately 25 hours before dosing, to CCI after dosing. Ten replicate 14-second ECG strips will be extracted from the continuous recording over a 5-minute time period preceding and up to the specified ECG acquisition time-point (see Section 10.2.1 for further details of ECG extraction and analysis).

Each 5-minute ECG strip extraction period will be preceded by an approximately 10-minute long fully supine rest period in an undisturbed environment without electronic devices (e.g., cellular telephone, tablet, computer) or television. Thus, participants will be supine and rested for at least 15 minutes leading up to each ECG extraction time point.

On Day –1, ECG strip extractions will be matched to the planned time of day of dosing (0 hour) and all planned post-dose ECG extraction timepoints (see SoA in Section 1.3). The Day –1 0-hour time point will serve as the time match for CCI post-dose.

Baseline ECG parameters will be determined from pre-dose ECG extractions at CCI CCI relative to dosing on Day 1.

Post-dose ECG strips will be extracted from the continuous recording at time points to match the PK sampling time points detailed in Section 8.5. ECG strips will be extracted before the time of actual PK sampling to avoid the influence of autonomic changes that may be associated with blood collection.

See Section 1.3 for details on the above timepoints.

When time points for assessments coincide, the order should be safety ECGs, vital signs, ECG strip extraction, then PK blood collection.

8.3.6. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical safety laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- 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 significant by the investigator or medical monitor.
  - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (see Section 10.3.1 and Section 10.3.2).
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology 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.

8.3.7. Pregnancy testing

- Refer to Section 5.1 - Inclusion criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at timepoints in the SoA during the study intervention period.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the clinical study.
- A serum or urine pregnancy test must be performed for all female participants of childbearing potential before the administration of the first 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.
- See Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.8. Study stopping / holding rules, safety monitoring AND/OR committee

- Participant safety will be continuously monitored by the medical monitor, designated Safety Lead (or delegate), safety review team throughout the study. In particular, data will be reviewed by the sponsor for identification of events that would potentially contribute to a requirement to pause/stop the study. It is not possible to outline what these events may be. However, SAEs and AEs with DAIDS Grade 3 and 4 considered associated with the supratherapeutic dose of the product will be kept under close scrutiny. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.

8.4. Adverse events, serious adverse events, and other safety reporting

For definitions relating to safety information see Section 10.3.

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

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.

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

All AEs/SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA.

AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) will be collected from the time a participant consents to participate in the study. Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

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 Section 10.3.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

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, after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.8 for contact information.

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 10.3.5.5 and/or Section 10.3.

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 Section 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 7.1.3.

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 clinical studies of ASOs. A monitoring strategy of renal function (e.g., serum creatinine, ACR) is presented in Section 7.1.4.

8.4.4.5. Injection Site Reactions

Injection site reactions were the most commonly reported treatment-related event in prior studies with bepirovirsen. Injection site reactions included, but were not limited to pain, erythema and pruritis. Injection site reactions will be assessed at all visits, and if present, should be reported as AEs.

8.4.5. Regulatory reporting requirements for SAEs

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. 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 10.3.5.3.
- 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 10 Timeframes for submitting SAE, pregnancy and other events 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*	electronic pregnancy report	24 hours*	electronic pregnancy 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, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

- 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 10 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 8.4.4. 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.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.7. CV and death events

This section is not applicable for this study as it is a healthy volunteer study.

8.4.8. Contact information for reporting SAEs, pregnancies and study holding rules

Table 11 Contact information for reporting SAEs, pregnancies and study holding rules

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 oax37649@gsk.com

8.4.9. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

- Plasma samples for pharmacokinetic analysis of bepirovirsen will be collected at the time points indicated in SoA (Section 1.3) at pre-dose (within 2 hours before dosing) and post-dose at:

CCI [redacted]

- 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). Plasma samples for PK analysis should be drawn immediately after ECG extractions and may be drawn within 10 minutes after the nominal time point to accommodate the ECG extractions. 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.
- Samples will be used to evaluate the PK of Bepirovirsen. Each PK blood sample will be processed into plasma and will be divided into 2 aliquots (1 each for PK and a backup). Samples collected for analyses of Bepirovirsen 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.
- Instructions for the collection and handling of biological samples will be provided by the sponsor.

8.6. Pharmacodynamics

Not applicable for this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

- CCI [redacted] (including CCI [redacted]) may be used to evaluate pharmacodynamic responses in healthy participants and assays related to the pathogenesis of chronic HBV infection and the participant's response to bepirovirsen.
- CCI [redacted] CCI [redacted] 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. The archived and remnant samples may be used as backup for assessments pre-specified in protocol or for the purpose of follow up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.). Other biomarkers may be evaluated as determined by emerging research and data.
- The archived samples may also be used for studying biomarkers that may be affected by treatment, or other immune-related responses.
- Additionally, samples may be used for further research by 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, research methods, or to develop tests/assays.
- Additional details of biomarker analysis will be provided in the biomarker analysis plan and the results will be documented in a separate report.

8.9. Immunogenicity assessments

Not applicable.

8.10. Health economics or medical resource utilization and health economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical hypothesis

The primary objective, as outlined in Section 3, is planned to be addressed using formal hypothesis testing. For the primary estimand, the following 1-sided hypothesis is planned to be tested for QT prolongation following the supratherapeutic single dose of bepirovirsen against a predefined threshold of 10 msec using the C-QTcF analysis:

CCI

CCI

Where ΔΔQTcF is the placebo-corrected QTcF change from baseline at the mean Cmax following supratherapeutic single dose of bepirovirsen.

Success criterion: CCI CCI at the mean Cmax following supratherapeutic single dose of CCI mg.

There is no formal hypothesis testing for the secondary objectives of evaluating the effect of bepirovirsen on other ECG parameters.

9.1.1. Multiplicity Adjustment

There is no adjustment for multiplicity.

9.2. Analysis sets

Table 12 Analysis sets

Analysis Set	Definition/Criteria	Main analyses in scope
Screened	• All participants who were screened for eligibility.	• Study population
Randomized	• All participants who were randomly assigned to study intervention in the clinical study. • The screened, enrolled, and randomized populations must be nested, i.e. the enrolled population must be a subset of the screened population, the randomized population must be a subset of the enrolled population.	• Study population
Safety/Exposed	• Participants who received study intervention. • Participants will be analyzed according to the study intervention administered.	• Safety

Analysis Set	Definition/Criteria	Main analyses in scope
QT/QTcF	All participants in the safety population with a valid ΔQTcF value (measurements at baseline as well as on-treatment with at least 1 post-dose time point). • Data will be reported according to the actual study intervention.	• Safety
PK	• All participants in the Safety Set who 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
PK/QTcF	All participants who were in both the QT/QTcF and PK populations with at least 1 pair of post-dose PK and ΔQTcF data from the same time point as well as participants in the QT/QTcF population who received placebo. • Data will be reported according to the actual study intervention.	• Concentration-QT

9.3. Statistical analyses

9.3.1. General considerations/definitions

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

All data will be available to view and descriptive analysis along with appropriate graphs will be provided. Categorical data shall be summarized by means of absolute and relative frequencies (counts and percentages) and continuous data by means of the number of observations, the arithmetic mean, standard deviation, minimum, median, maximum, CI, geometric mean and coefficient of variation as appropriate.

9.3.2. Primary estimand analyses

9.3.2.1. Definition of endpoint

The primary endpoint is the change from baseline in Fridericia heart-rate-corrected QT interval (QTcF) under bepirovirsen exposure following a supratherapeutic single dose.

9.3.2.2. Main analytical approach

CCI [redacted]

CCI
CCI
CCI
CCI

The Cmax following the therapeutic single dose of 300 mg has been estimated from previous studies and the Pop PK model. The geometric mean of the individual Cmax values for participants following the supratherapeutic single dose of CCI mg will be calculated from data collected. CCI
CCI
CCI
CCI The summary measure of the study is the mean and 90% CI of the predicted ΔΔQTcF at geometric mean Cmax following a supratherapeutic single dose of CCI mg of bepirovirsen. CCI
CCI
CCI
CCI
CCI

CCI
CCI
CCI
CCI
CCI
CCI CCI
CCI
CCI

To assess the appropriateness of a linear model, normal quantile-quantile plots for the standardized residuals will be evaluated. In addition, plots of standardized residuals versus concentration, baseline QTcF, nominal time, and active treatment will be produced. Scatter plots for standard residuals versus continuous covariates and box plots for standard residuals versus discrete covariates will be provided. A scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and a linear regression line will also be produced to evaluate the assumption of a linear C-QTcF relationship. If there is an indication that a linear model is inappropriate, additional models will be fitted, in particular an Emax model. The C-QTcF analysis will be repeated for the model found to best accommodate the observed relationship.

Further details of this analysis will be described in Statistical Analysis Plan.

9.3.3. Secondary estimands analyses

- The summary of the change from baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR, and ΔQRS) intervals will be provided by dose and time point with and without outliers when applicable.
- Categorical outliers of QTcF, HR, PR and QRS will be summarized separately for CCI mg and CCI mg in frequency tables with counts (percentages) for both number of participants and number of time points. The number (percentage) of participants as well as time points who had increases in absolute QTcF interval values >450 and ≤480 ms, >480 and ≤500 ms, and >500 ms, and changes from pre-dose baseline of >30 and ≤60 ms, and >60 ms; increase in PR interval from pre-dose baseline >25% to a PR >200 ms; increase in QRS interval from pre-dose baseline >25% to a QRS >120 ms; decrease in HR from pre-dose baseline >25% to a HR <50 bpm; and increase in HR from pre-dose baseline >25% to a HR >100 bpm will be determined.
- For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point. Frequency counts and percentage of treatment emergent changes of T wave morphology and U-wave presence will be summarized separately for CCI mg and CCI mg.
- The summary statistics of the plasma concentrations and selected PK parameters of bepirovirsen CCI mg and CCI mg will be provided as follows: geometric mean and geometric %CV will be calculated for AUC(0-24), AUC(0-∞), Cmax and median and range for Tmax.

9.3.4. Safety endpoint(s) analyses

Safety parameters such as occurrence of AEs and SAEs, change from baseline in clinical laboratory tests and vital signs will be descriptively summarized separately for CCI mg and CCI mg as appropriate. All safety analyses will be performed on the safety population.

The following summaries of AEs will be provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment-related AEs
- Incidence and severity of AESIs
- Incidence of SAEs

9.4. Interim analyses

No interim analysis is planned for this study.

9.5. Sample size determination

A sample size of approximately 46 participants with 1:1 randomization is chosen to obtain 42 evaluable participants to complete the study under the original design of receiving a single dose of either placebo or CCI mg bepirovirsen. A size of 42 evaluable participants with concentration and ΔQTcF measured around Cmax provides at least 90% power to exclude that active drug caused more than a 10-msec QTcF effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% CI of the model-predicted QTcF effect at the observed geometric mean Cmax of active drug in the study.

This power is approximated using a non-paired t-test. CCI

A Monte Carlo simulation analysis was used to determine the probability of the 90% upper limit of the CI of the ΔQTcF at the geometric mean of the Cmax following a supratherapeutic dose of CCI or CCI mg encompassing the CCI cut-off value. Based on this simulation approach, it is expected that under the assumptions of no true effect or a small effect of CCI on QTcF at the CCI mg and proportionally at CCI mg dose of bepirovirsen, the expected probability of incorrectly detecting an effect CCI CCI) is <1 % (false positive) with 42 evaluable participants.

Table 13 Sample Size Determination - Power

CCI

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 international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB 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), 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 sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection (e.g., HIPAA and GDPR requirements), where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- 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 copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining samples for optional further research related and not related to this study. The investigator or authorized designee will explain to each participant the objectives of the further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

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

10.1.4. Recruitment strategy

Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

10.1.5. 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 their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK, third parties working on behalf of GSK, and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

- A SRT is in place for each GSK product. It comprises 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.

10.1.7. 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 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 6 months of primary/study completion date (pediatric population) and within 12 months of primary/ study completion date (adult population). 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 layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- 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. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The 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 Document 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 non-compliance 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 a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. 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. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

10.1.9. Source documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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 Monitoring Guidelines.
- 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.

- Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of source data shared may include, discharge summaries, imaging reports, scans, videos, pathology reports, biological specimens, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

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.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 14 will be performed by the central laboratory.
- 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 safety laboratory report.
- The addresses of the clinical laboratories in charge of the testing can be found in the "Oversight Vendor management plan".

Table 14 Protocol-required safety laboratory tests

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet Count</td><td rowspan="4">RBC Indices:
MCV
MCH</td><td rowspan="4">WBC count (with Differential if WBC abnormal):
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>RBC Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td>Clinical Chemistry[4]</td><td>Blood Urea Nitrogen</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase</td><td>Total, indirect, and direct bilirubin</td></tr>
</table>

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td></td><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase</td><td>Total Protein</td></tr>
<tr><td></td><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase[5]</td><td>Albumin</td></tr>
<tr><td></td><td></td><td>Magnesium</td><td></td><td></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• By dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Tests</td><td colspan="4">• Follicle-stimulating hormone
• Serology (HIV antibody, HBsAg, HbcAb, hepatitis C virus antibody)
• Highly sensitive urine or serum hCG pregnancy test (as needed for women of childbearing potential)[1]
• Other laboratory: Coagulation Panel (PT, INR, APTT), p-ANCA, c-ANCA (MPO-ANCA, PR3-ANCA)[2], Complement factors C3, C4, Rheumatoid factor, hs-CRP
• Urine ACR
• Drug, alcohol and cotinine screen
• PK samples</td></tr>
<tr><td rowspan="4">Additional tests listed under safety follow-up processes</td><td colspan="4"><u>Liver Chemistry Stopping Criteria[3]</u>
• Viral hepatitis serology (Hepatitis A IgM; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody, EBV capsid antigen IgM antibody (or if 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 (IgG or gamma globulins).
• Serum acetaminophen adduct HPLC assay</td></tr>
<tr><td colspan="4"><u>Drug Induced Vascular Injury and Complement Monitoring Criteria</u>
• CH50
• Factor Bb level
• Factor H level
• sC5b-9
• cryoglobulins[4]
• SPEP, UPEP
• hs-CRP</td></tr>
<tr><td colspan="4"><u>Hematological Monitoring Criteria</u>
• anti-platelet antibodies</td></tr>
<tr><td colspan="4"><u>Drug Induced Kidney Injury Monitoring Criteria</u>
• 24-hour urine analysis
• renal ultrasound
• urine microscopy
• serum urea and creatinine
• platelets
• urgent serum vasculitis screen (including ANCA, ANA, dsDNA, cryoglobulins[4])
• SPEP/UPEP
• complement panel (C3, C4, C5a, and Bb)
• eGFR*</td></tr>
<tr><td colspan="5">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. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver monitoring event are given in Section 7.1.1. Liver event stopping criteria and Section 10.5 Liver safety requirements</td></tr>
</table>

Laboratory Assessments	Parameters
and guidelines]. All events of ALT [or AST] ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT [or AST] ≥3 × ULN and INR >1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in 24 hours (excluding studies of hepatic impairment or cirrhosis). 4. Cryoglobulins to be tested locally if available 5. If alkaline phosphatase is elevated, consider fractionating. Note: The investigator must document their review of each laboratory safety report. * To assess the kidney function, use the eGFR 2021 calculator.	

10.2.1. Continuous Holter Monitoring

ECGs to be used in the analyses will be extracted at pre-determined time points as defined in the Schedule of Assessments (Section 1.3) and will be read centrally by the vendor by readers blinded to the subject and treatment allocation.

Baseline and post-dose ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.

The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods that will be employed:

ECG Extraction Technique

Ten 14-second digital 12-lead ECG strips will be extracted from the continuous Holter recordings using a computer-assisted process utilized by the vendor. This method enables extraction of ECGs with the lowest HR variability and noise within the specified extraction time window. The ECG replicates will be extracted over the last 5 minutes of the 15-minute supine rest period (see Section 8.3.5) preceding the extraction time points.

QT Analysis

QT analysis will be performed for all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures will be used to identify "high" and "low" confidence beats, based on biologically plausible thresholds and beat to beat variability.

Computer-assisted measurement of primary ECG parameters (QT, QTcF, RR) will be performed for all recorded beats that are deemed "high confidence". All low confidence beats will be reviewed manually and adjudicated. The final QC assessment is performed by a cardiologist. Beats found acceptable by manual review will be included in the analysis. The median QT, QTcF, and RR value from each extracted replicate will be calculated. The mean of all available medians from a nominal timepoint will then be used as the participant's reported value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes that are not present in the pre-dose ECGs. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any

replicates at the time point. For pre-dose, the category will be deemed as present if observed in any replicates from any time points (see Section 8.3.5).

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 that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
Events NOT 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 ≥3×ULN AND total bilirubin ≥2×ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2×ULN, and direct bilirubin ≥2×ULN and at least doubled from baseline value) 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. Unsolicited AE

• Definition of unsolicited AE
• An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.4. 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.

10.3.5. Recording, assessment, and follow-up of AEs, SAEs, and pregnancies

10.3.5.1. 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 sponsor's 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 identifier, 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.

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, SAE, 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.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. 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 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 sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. 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).

10.3.5.5. 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 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.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to 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.

Follow-up during the study

AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study. If a new AESI is identified at the last study visit, it is required to be followed up for up to 30 days, or sooner if resolved, stabilised, otherwise explained or the participant is lost to follow-up.

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 10.3.5.7.

10.3.5.6. Updating of SAE, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, or pregnancy 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 (see Section 8.4.3).

10.3.5.7. Reporting of SAEs, and pregnancies

SAE reporting to sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to 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 sponsor/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 product that is not part of the study design, 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 8.4.8.

SAE reporting to sponsor via paper data collection tool

- Email/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 email/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 8.4.8.

10.3.6. 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/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. 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. WONCBP

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal).
- Permanently sterile due to 1 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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 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 clinical study include:
Highly effective methods[b] that have low user dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b].
• IUD.
• IUS[b].
• Bilateral tubal occlusion/ligation.
• 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 WOCBP, and the absence of sperm has been confirmed. (e.g., medical assessment of the surgical success for vasectomy). If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation for a male partner can come from medical history interview with the participant.
Highly effective methods[b] that are user dependent Failure rate of <1% per year when used consistently and correctly.
• 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 clinical 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 CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Liver safety requirements and guidelines

10.5.1. Liver safety: required actions, monitoring, and follow-up to assess causality of liver event

Table 15 Required actions, monitoring, and follow-up to assess causality of liver event

<table>
<tr><th colspan="2">Liver event increased monitoring criteria</th></tr>
<tr><td>ALT absolute</td><td>ALT ≥3xULN.
If ALT ≥3xULN AND total bilirubin[1,2] ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN AND INR >1.5, report as an SAE.</td></tr>
<tr><th colspan="2">Required actions, monitoring and follow-up to assess causality of liver event</th></tr>
<tr><th>Actions and monitoring</th><th>Follow-up to assess causality of liver event</th></tr>
<tr><td>• Report the event to GSK within 24 hours.
• Complete the liver event form, and complete SAE data collection tool if the event also meets the criteria for an SAE[2].
• Perform liver event follow-up to assess causality of liver event.
• Monitor the participant liver chemistries (see MONITORING).
For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study intervention.
<u>MONITORING:</u>
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 to assess liver event causality within 24 hours.
• Monitor participants twice weekly until liver chemistries reduce to <3xULN for ALT, <2xULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits.
• A specialist or hepatology consultation is recommended.
If ALT ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within 24-72 hours.</td><td>• Viral serology[3].
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (IgG or gamma globulins).
• Blood sample for PK analysis, obtained as soon as possible following the occurrence of an event[4].
• Serum CPK and LDH, GGT, GLDH, and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2xULN.
• Obtain complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form.
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form.
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:
• Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout).
Serum acetaminophen adduct assay may be omitted from protocols for residential HV studies where the participant does not leave the clinical unit during the period of study intervention dosing.
• Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease, complete liver imaging forms.
• Liver biopsy may be considered and discussed with local specialists if available, for instance:
– In patients when serology raises the possibility of AIH.</td></tr>
</table>

Liver event increased monitoring criteria	
ALT absolute	**ALT ≥3xULN.** **If ALT ≥3xULN AND total bilirubin[1,2] ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN AND INR >1.5, report as an SAE.**
Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
• Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits.	– In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention. – In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible).
4. Record the date/time of the PK blood sample draw and the date/time of the dose of study intervention prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

10.5.2. Liver safety: liver chemistry increased monitoring criteria with continued study intervention

Not applicable.

10.5.3. Liver safety: study intervention restart and/or rechallenge guidelines

Not applicable.

10.6. Appendix 6: Protocol Amendment History

DOCUMENT HISTORY	
Amendment 2	15 Nov 2024
Amendment 1	07 June 2024
Original Protocol	12 March 2024

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 1 (07 June 2024)

CCI

[redacted]

CCI

[redacted]

11. REFERENCES

Bepirovirsen Investigator Brochure. GSK Document Number RPS-CLIN-047928. Version 05, 06-Jul-2023.

Chi X, Gatti P, Papoian T. Safety of antisense oligonucleotide and siRNA-based therapeutics, Drug Discovery Today. 2017;22(5):823-33.

Clinical Study Report, Study 213725. ISIS Study Number 505358-CS1. A Blinded, Placebo-Controlled, Dose-Escalation, Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of ISIS 505358 (an Inhibitor of Hepatitis B Virus Surface Antigen) in Healthy Volunteers. August 2015.

Clinical Study Report, Study 205695. Formerly ISIS 505358-CS3. GSK Document Number 2020N429086_00. A Phase 2, Double-Blinded, Randomized, Placebo-Controlled, Dose-Escalation Study to Examine the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ISIS 505358 in Treatment-Naïve Patients with Chronic Hepatitis B Virus Infection. August 2020.

Clinical Study Report, Study 209668. Phase 2b multi-center, randomised, partial-blind parallel cohort study to assess the efficacy and safety of treatment with bepirovirsen in participants with chronic hepatitis B virus (B-Clear). March 2023.

Clinical Study Report, Study V72411G. GSK Document Number 2022N503330_00. Effects on hERG Tail Current Recorded from Stably Transfected Human Embryonic Kidney Cells. May 2022.

Clinical Study Report, Study 209348. A Phase IIb Multi-Center, Randomised, Open Label Study to Assess the Efficacy and Safety of Sequential Treatment with GSK3228836 followed by Pegylated Interferon Alpha 2a in Participants with Chronic Hepatitis B Virus (B-Together). February 2023.

Crooke ST, Baker BF, Wiztum JL, et al. The effects of 2'-O-Methoxyethyl containing antisense oligonucleotides on platelets in human clinical trials. Nucleic Acid Ther. 2017;27(3):121-9.

Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0. National Institutes of Health; Institute of Allergy and Infectious Diseases, Bethesda, MD; 2017. Available at: https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one

Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry: E14 Clinical Evaluation of QT/QTcF Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005 [cited 25 Jan 2020] [20 screens]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf

Flaim JD, Grundy JS, Baker BF,et al. Changes in mipomersen dosing regimen provide similar exposure with improved tolerability in randomized placebo-controlled study of healthy volunteers. J Am Heart Assoc 2014 Mar 13; 3(2): e000560

Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTcF modeling [published correction appears in J Pharmacokinet Pharmacodyn. 2018 Jan 12;:]. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

GSK Document Number 2019N419364_01. A 39-Week Repeat Dose Toxicity Study of ISIS 505358 in Cynomolgus Monkeys with a 26-Week Recovery. November 2015.

GSK Document Number 14928069. Clinical Pharmacology Modelling Report - Population Pharmacokinetic Analyses for Bepirovirsen **(**GSK3228836**)** in Healthy Participants and Participants with Chronic Hepatitis B Infection (Phase 1 and Phase 2). March 2023.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. E14/S7B Questions and Answers: Clinical and Nonclinical Evaluation of QT/QTcF Interval Prolongation and Proarrhythmic Potential. Training Materials. March 2022. https://database.ich.org/sites/default/files/ICH_E14-S7B_TrainingMaterial_2022_0407.pdf

Yuen MF, Heo J, Jang JW, et al. Safety, tolerability and antiviral activity of the antisense oligonucleotide bepirovirsen in patients with chronic hepatitis B: a phase 2 randomized controlled trial. Nat Med. 2021;27(10):1725-34.

Signature Page for 205873 TMF-19984209 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 15-Nov-2024 18:33:07 GMT+0000

Signature Page for TMF-19984209 v1.0