TITLE PAGE

Protocol Title:

Four-part, Randomized, Double-blind (Parts 1, 2A, 3 and 4), Multi-center, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection

Protocol Number: 214760 /Amendment 10

Compound Numbers: GSK3965193, Bepirovirsen (GSK3228836)

Brief Title: Phase 1/2 Study of GSK3965193 in Healthy Participants and Participants Living with Chronic Hepatitis B Infection

Study Phase: Phase 1/Phase 2a

Sponsor Name and Legal Registered Address:

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Middlesex, TW8 9GS
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Regulatory Agency Identifying Number(s):

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

Sponsor Signatory:

Teresa Wright, MD
VP, Clinical Research Head
Hepatology, Respiratory and Immunology Clinical Research

Approval Date: 17 Mar 2025

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Protocol Amendment 10 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	214760
EudraCT number	2021-005117-13
EU CT number	2023-509684-24
Approval date	17 Mar 2025
Title	Four-part, Randomized, Double-blind (Parts 1, 2A, 3 and 4), Multi-center, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 10	17 Mar 2025	TMF-20900398
Amendment 09	22 July 2024	TMF-19627189
Amendment 08	26 March 2024	TMF-18847281
Amendment 07	29 January 2024	TMF-18464535
Amendment 06	01 December 2023	TMF-15764438
Amendment 05	09 March 23	TMF-15668213
Amendment 04	06 December 22	TMF-15149599
Amendment 03	26 August 22	TMF-14896668
Amendment 02	25 April 22	TMF-14610019
Amendment 01	31 March 22	TMF-14546127
Original Protocol 00	26 January 2022	TMF-14044538

Amendment 10: 17 Mar 2025

Overall rationale for the Amendment:

The reasons for this amendment are as follows:

- To align the summary of identified and potential risks of clinical significance with update to the Bepirovirsen Investigator's Brochure v.06 dated 16JAN2025.
- To make minor modifications for clarity and consistency with other bepirovirsen trials.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and Name	Description of Change	Brief Rationale
2.3. Benefit/Risk Assessment	Edited introductory sentence to clarify that more detailed and the latest information on the benefit/risk assessment, and identified and potential risks can be found in the Investigator's Brochure.	To clarify that the IB has more detailed and current information on the benefit/risk assessment for reference.
2.3.1. Risk Assessment	Updated to align with the current Investigator's Brochure and for consistency with other bepirovirsen trials.	To align the summary of identified and potential risks of clinical significance with recent IB update, and with other bepirovirsen protocols.
1.3.4 Part 3 Schedule of Activities 1.3.9 Part 4 Schedule of Activities 5.2.2 Exclusion Criteria for PLWCHB	Clarifying that Covid testing must be performed as per the schedule of activities, and that the method of testing should be in accordance with local site procedures.	To add clarity and avoid potential protocol deviations.
5.3.2. Lifestyle Considerations: Caffeine, Alcohol, and Tobacco	Clarify the following restriction applies to Parts 1 and 2 only: "During each visit, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or PD sample."	This restriction is not considered necessary for Parts 3 and 4.
8.3.7.2.2. Vascular Inflammation and Complement Activation	Title changed to 'Vascular Inflammation and Complement Activation and Other Immune mediated events'.	For consistency with other bepirovirsen trials.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Four-part, Randomized, Double-blind (Parts 1, 2A, 3 and 4), Multi-center, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection

Brief Title: Phase 1/2 Study of GSK3965193 in Healthy Participants and Participants Living with Chronic Hepatitis B Infection

Rationale:

HBV infection, especially chronic infection, is a significant worldwide medical problem. Globally, in 2015, an estimated 257 million people were living with chronic Hepatitis B. Current CHB therapies are inefficient due to their inability to lower the high levels of immunosuppressive hepatitis B virus (HBV) antigens such as hepatitis B surface antigen (HBsAg) which are hypothesised to attenuate HBV-specific immunity. Functional cure for HBV will require a combination of approaches targeting viral replication and immunomodulation in order to restore HBV-specific immune responsiveness [World Health Organization (WHO), 2015].

GSK3965193 is an orally bioavailable small molecule inhibitor of human non-canonical poly A RNA polymerases PAPD5 and PAPD7 (PAPD5/7). HBV utilizes PAPD5/7 for viral messenger ribonucleic acid (mRNA) stabilization [Mueller, 2019]. PAPD5/7 inhibition has demonstrated the reduction of HBsAg preclinically by 1 log10 IU/mL via accelerated viral RNA degradation [Mueller, 2019].

Bepirovirsen is an antisense oligonucleotide (ASO) currently in Phase 3 development for functional cure of CHB infection. This molecule directly targets all HBV mRNAs via Ribonuclease H (Rnase H) mediated degradation, resulting in the reduction of HBsAg for as much as >3 log10 IU/mL in a Phase 2a study [Yuen, 2021].

This Phase 1/2a multiple part study is a first-time-in-human (FTIH) study designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of single (Part 1) and repeat doses (Part 2) of GSK3965193 in healthy participants. Part 3 will evaluate the ability of GSK3965193 to lower HBsAg in participants living with chronic hepatitis B infection (PLWCHB). Part 4 will evaluate the safety and tolerability of combination therapy with GSK3965193 and bepirovirsen and the potential to effect sustained virologic response in PLWCHB.

Objectives and Endpoints:

Objectives	Endpoints
Part 1 and Part 2 (healthy participants)	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Part 2)
• To evaluate the PK characteristics of single and repeat doses of GSK3965193	• Area under the plasma-concentration time curve (AUC): $AUC_{(0-\infty)}$ for single dose and $AUC_{(0-tau)}$ for repeat dose. • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (T1/2) will be calculated as data permits per part
Secondary	
• To investigate the effect of food on the PK characteristics of CCI [redacted] of GSK3965193	• Area under the plasma-concentration time curve (AUC): $AUC_{(0-\infty)}$, and maximum observed plasma drug concentration (Cmax) as data permits
Part 3 and Part 4 (participants living with chronic hepatitis B infection [PLWCHB])	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193 monotherapy (Part 3) and in combination with bepirovirsen (Part 4)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, and cardiac parameters (ECG), sensory nerve conduction

Objectives	Endpoints
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• Maximum reduction of serum HBsAg levels from baseline CCI [redacted]
• To evaluate efficacy of GSK3965193 in combination with bepirovirsen in PLWCHB (Part 4)	• Achieving complete response (serum HBV DNA and HBsAg <LLOQ for 6 consecutive months after the planned end of treatment of bepirovirsen)
Secondary	
• To evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB (Part 3)	• $AUC_{(0\text{-}tau)}$, Cmax, Tmax, and apparent terminal T1/2 will be calculated as data permits
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• ≥ 0.5 x log IU/mL reduction of serum HBsAg levels from baseline anytime during the study (on-treatment and post-treatment)
• To assess the safety and tolerability of bepirovirsen monotherapy in PLWCHB (Part 3)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis) and vital signs
• To evaluate PD effect of GSK3965193 in combination with bepirovirsen in PLWCHB (Part 4)	• HBsAg loss (defined by two consecutive measurements of HBsAg below the limit of quantification) anytime during the study (on-treatment and post-treatment)

Overall Design:

This study is a 4-part, randomized, double-blind, multi-center, placebo-controlled study to assess the safety, tolerability, PK, and PD of GSK3965193 monotherapy in healthy participants; and GSK3965193 as monotherapy or in combination with bepirovirsen in PLWCHB.

- Part 1 was CCI [redacted] of healthy participants. This part has completed.
- Part 2 was composed of two sub-parts (Part 2A and Part 2B) and has completed. Part 2A was a CCI [redacted] separate cohorts of healthy participants who are not enrolled in Part 1 of the study.

Part 2B was a CCI to evaluate the effect of food and CCI on the PK CCI of GSK3965193 in a cohort of healthy participants who were not enrolled in either Part 1 or Part 2A of the study.

- Part 3 is CCI, repeat dose study with CCI GSK3965193 or placebo in 1 cohort of PLWCHB on stable nucleos(t)ide analog (NA) therapy. CCI
- Part 4 is a repeat dose study with 1 dose level of GSK3965193 or placebo administered for CCI

Brief Summary:

The objectives of this phase 1/2a study are to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK3965193 monotherapy in healthy participants and PLWCHB. In addition, this study will also evaluate if treatment of GSK3965193 in combination of bepirovirsen can achieve a complete response in PLWCHB.

Number of Participants:

Approximately CCI participants will be enrolled and randomized as follows. This study may enrol additional participants to within CCI of the planned total in each part to ensure adequate PK and/or PD data are available for analysis.

Part 1: CCI
Part 2:
Part 3:
Part 4:

Intervention Groups and Duration:

In all parts except for Part 2B (open label), participants who meet the criteria for study entry will be randomised to receive GSK3965193 (active) or placebo before study intervention administration on Day 1.

Part 1

Part 1 assessed single ascending doses of GSK3965193 CCI in two sequential cohorts (Cohorts 1 and 2) of healthy participants. Participants received single ascending doses of GSK3965193 or matching placebo CCI The starting dose was CCI. The initial dosing for all periods was staggered so that 2 participants were dosed as sentinel participants, CCI. After approximately 24 hours, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period were dosed.

Participants were enrolled for approximately CCI [redacted]

Part 2 (A and B)

Part 2A

Part 2A assessed repeat doses of GSK3965193 across CCI [redacted] of CCI healthy participants per cohort. Participants were randomized to receive either GSK3965193 or placebo as CCI [redacted] for 14 days. During dose escalation, each cohort was staggered so that only CCI of the CCI participants were administered study drug initially as sentinel participants CCI [redacted] After at least 3 days of dosing, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the cohort were dosed.

Part 2A started while Part 1 was ongoing. The doses selected for Part 2A were based on CCI [redacted]. Part 2A has enrolled three cohorts of participants CCI [redacted] who received CCI [redacted], respectively.

Participants were enrolled for approximately CCI [redacted]

Part 2B

Part 2B assessed CCI [redacted] of GSK3965193 under CCI [redacted]. Participants received CCI [redacted] GSK3965193 (open label) CCI [redacted]. These two periods were CCI [redacted] GSK3965193 tablets CCI [redacted]

Participants were enrolled for approximately CCI [redacted]

Part 3

Part 3 will assess repeat doses of GSK3965193 in CCI [redacted] of PLWCHB on stable NA therapy. CCI [redacted] receive either GSK3965193 or placebo as CCI [redacted] The dose of GSK3965193 for Part 3 CCI [redacted]

After GSK3965193 or placebo dosing and 2 weeks of washout, participants in this cohort with screening HBsAg levels CCI will be given the option to continue in the study and CCI bepirovirsen treatment. Participants can enroll in Part 3 even if they choose not to receive bepirovirsen.

Participants who do not participate in the optional bepirovirsen treatment will be enrolled for approximately CCI
Participants who opt to continue with bepirovirsen treatment will be enrolled for approximately CCI

Part 4

Part 4 will assess repeat doses of GSK3965193 dosed concurrently with bepirovirsen in a CCI of PLWCHB on stable NA therapy CCI participants will be randomized in a CCI to receive either GSK3965193 or placebo CCI The dose of GSK3965193 CCI
Bepirovirsen dosing will continue CCI after GSK3965193 or placebo dosing completes.

Participants will be enrolled for approximately CCI , and approximately CCI

Data Monitoring/ Other Committee: Yes

CCI

1.2. Schema

CCI

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

1.3. Schedules of Activities (SoA)

1.3.1. Part 1 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

1.3.2. Part 2A – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.3.3. Part 2B – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

1.3.4. Part 3 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.3.5. Part 3 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

1.3.6. Part 3 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

1.3.7. Part 3 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

1.3.8. Part 3 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

1.3.9. Part 4 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.3.10. Part 4 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

1.3.11. Part 4 – CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

GSK3965193 is an orally bioavailable small molecule inhibitor that is being developed for the treatment of chronic hepatitis B virus infection. This Phase 1/2a study is a first-time-in-human (FTIH) study designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and repeat doses of GSK3965193 in healthy participants. A third part will evaluate the ability of GSK3965193 to lower hepatitis B surface antigen (HBsAg) in participants living with chronic hepatitis B (PLWCHB). A fourth part will evaluate the safety and tolerability of combination therapy with GSK3965193 and bepirovirsen and the potential to effect complete response in PLWCHB.

Data from this study will provide an assessment of the safety, tolerability, pharmacokinetic and pharmacodynamic outcomes of GSK3965193 administered alone and in combination with bepirovirsen, thus supporting subsequent clinical studies.

2.2. Background

Chronic Hepatitis B (CHB) is a global public health problem and a major cause of life-threatening liver cirrhosis and hepatocellular carcinoma. Current CHB therapies are inefficient in delivering sustained virologic response potentially due to their inability to lower the high levels of immunosuppressive hepatitis B virus (HBV) antigens such as HBsAg which are hypothesised to attenuate HBV-specific immunity [World Health Organization (WHO), 2015].

GSK3965193 is an orally bioavailable small molecule inhibitor of the human non-canonical poly A RNA polymerases PAPD5 and PAPD7 (PAPD5/7). *In vitro* and *in vivo* models have demonstrated that inhibition or knock down of PAPD5/7 resulted in a reduction of HBsAg through accelerated viral RNA degradation [Mueller, 2019]. Suppression of HBV antigens, with one or more agents such as GSK3965193, is a key goal of any therapeutic regimen aimed at sustained virologic response.

Bepirovirsen is an antisense oligonucleotide (ASO) currently in Phase 3 development for functional cure of CHB infection. This molecule was designed to inhibit the synthesis of HBsAg without having a direct effect on covalently closed circular HBV DNA or integrated HBV DNA. Bepirovirsen directly targets all HBV mRNAs via Ribonuclease H (RNase H) mediated degradation, resulting in the reduction of viral proteins including HBsAg. In a Phase 2a study [Yuen, 2021], 7 of 12 (58%) treatment-naïve PLWCHB dosed with 300 mg bepirovirsen over 4 weeks experienced a ≥0.5 log10 reduction in HBsAg by Day 29. In the same study, 3 of 5 (60%) PLWCHB on stable nucleos(t)ide analogue (NA) therapy treated with 300 mg bepirovirsen achieved HBsAg reductions >3 log10 IU/mL. In a Phase 2b study [Yuen, 2022], 9 to 10% of PLWCHB on stable NA therapy who were treated with 300 mg bepirovirsen over 24 weeks demonstrated a decline in HBV DNA to <LLOQ and to undetectable levels (target not detected; TND) and HBsAg to <LLOD, and this virologic response was sustained for up to 24 weeks

after treatment was stopped. Preclinically, combination of GSK3965193 with bepirovirsen has demonstrated an additive effect in reducing HBsAg levels.

Parts 1 and 2 have completed. Dosing of GSK3965193 in PLWCHB either as monotherapy or in combination with bepirovirsen has not commenced as of the data cut-off (09th October 2023). A summary of adverse events (AEs) is included in the GSK3965193 Investigator's Brochure.

Clinical safety data obtained during Parts 1 and 2 were reviewed during preparation of Investigator's Brochure V02 (last data cut-off October 2023). There were no important identified risks associated with GSK3965193 which would preclude further development.

2.3. Benefit/Risk Assessment

More detailed and the latest information about the known and expected benefits and risks and reasonably expected adverse events of GSK3965193 and bepirovirsen may be found in the Investigator's Brochures.

Details of these risks, as well as the risks associated with the procedures, and the proposed strategy to mitigate/monitor these risks are detailed in Section 2.3.1.

2.3.1. Risk Assessment

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK3965193		
Peripheral neuropathy	CCI [redacted]	**General Measures:** Peripheral neuropathy events are categorized as Adverse Events of Special interest (AESIs) which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. **Participant selection:** Appropriate exclusion criteria are included in the protocol (Section 5.2) to exclude patients with neuropathy or at high risk of neuropathy. **Monitoring & Stopping Criteria:** Proposed Monitoring and Stopping rules for potential drug-induced neuropathy (see Section 7.1.4).

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	
Headache	Clinical: During Part 2A (multiple ascending doses), some participants experienced grade 1 events of headache that were assessed as possibly related to study medication. Given the frequency of headache in the healthy volunteer population particularly in the context of a prolonged overnight fast, a causal relationship between GSK3965193	**Monitoring Criteria:** Participants will be monitored for headache. Baseline collection of migraine-related neuropeptides for all subjects; repeat sample collection and testing of all samples in symptomatic participants experiencing ≥ Grade 2 headache.

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	has not been established. Headache will be monitored closely during the clinical trial.	
Neurocognitive symptoms	Clinical: During Part 2A (multiple ascending doses) of Study 214760, neurocognitive symptoms such as feeling of 'hangover', brain fog, nightmare and drowsiness were reported. A clear causal relationship between these events and GSK3965193 has not been established; however, these types of events will be closely monitored, and appropriate risk mitigation has been included in the protocol.	**General Measures:** Neurocognitive events are categorized as Adverse Events of Special interest (AESIs) which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. **Monitoring & Stopping Criteria:** Assess baseline cognition using the Modified Mini-Mental Status Exam (MMSE). Repeat testing should be performed at the discretion of the Investigator should any concerns be raised alongside an assessment as to whether study treatment should be discontinued. Individual participant and study level stopping criteria are defined in Section 7.1.4 as are sponsor actions taken in response to study stopping. ,

Signals or Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
ECG effects	CCI [redacted] Clinical: No clinically significant treatment emergent ECG abnormalities have been observed in the clinical study at the time of the IB data cut-off (11 April 2023).	**Monitoring:** ECG and vital signs measurements included in all parts as outlined in the SoA tables; telemetry and Holter monitoring were included in Parts 1 and 2

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effect on human embryo/fetus	Nonclinical: Preliminary animal embryofetal studies suggest minimal risk for the developing human embryo or fetus at the proposed clinical dose range. Women of childbearing potential (WOCBP) can receive GSK3965193 in a clinical study if they use proper contraception as required by the study protocol to avoid pregnancy while taking part in the study.	Pregnant women will not be eligible to participate. Participating WOCBP (applicable to Parts 3 and 4 only) will agree to comply with the study contraception requirements. Participants will be withdrawn from the study if the participants become pregnant during the study. Pregnancy tests will be done at screening, before dosing, and after completion of dosing. Refer to Section 10.4.3 for detailed information regarding collection of pregnancy information
Bepirovirsen		
Drug induced vascular inflammation and complement activation (DIVI)	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. Clinical studies conducted with Bepirovirsen to date have reported increased C-reactive protein levels, influenza-like symptoms (fever, chills, arthralgia, myalgia, headache) and decreased	**Monitoring & Stopping Criteria** **Laboratory Evaluations:** Inclusion of tests for biomarkers of inflammation/complement activation that would be expected to accompany vascular injury to be taken at the time of a clinical event suggestive of vasculitis and/or immune activation and compared to referenced baseline measurements. **Stopping Criteria:** Proposed Monitoring Schedule and Stopping Rules for Drug Induced Vascular Injury and Complement Activation (see Section 7.1.6)

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	complement factors C3 and C4, indicating an inflammatory response. Additionally, events consistent with cryoglobulinemic vasculitis/ type II cryoglobulinaemia have been noted. These were described by dermatological and rheumatological events. Serious adverse inflammatory and immune reactions such as immune thrombocytopenia, auto-immune hemolytic anemia, systemic inflammatory response syndrome, and a mild cryoglobulinemic flare have also been documented.	
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	**Monitoring & Stopping Criteria:** Periodic liver function assessments will include AST, ALT, alkaline phosphatase, and bilirubin will be performed during the different parts of the study. **Stopping Criteria:** ALT flares are expected in both Part 3 and Part 4 due to bepirovirsen. Monitoring, hold and stopping criteria are presented in Section 7.1.1.

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	degeneration in mice, consistent with findings noted with other 2'-methoxyethyl (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. In the Phase 2a CCI [redacted] and Phase 2b CCI [redacted] studies in patients with chronic HBV infection, ALT increases (defined as ALT >3x ULN) were associated with either a preceding or concurrent decline in HBsAg. Review of AE data and laboratory data in more than CCI participants showed no evidence of DILI. The likelihood is that ALT increases are an indication of therapeutic effect.	

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia leading to clinically significant bleeding events	Two types of thrombocytopenia have been described for the 2'-MOE ASOs [Chi,2017; Crooke, 2017]. One type is a rapid onset, unpredictable thrombocytopenia. The other more common type is characterised by a gradual decline in platelets leading to mild to severe thrombocytopenia and can be asymptomatic or associated with mild to severe bleeding. In monkeys given bepirovirsen, there were incidences of both types in a 39-week study. Thrombocytopenia was not reported in the Phase 1 CCI [redacted] or Phase 2a CCI [redacted] clinical studies. In the Phase 2b CCI [redacted] participants had platelet counts CCI [redacted] during the treatment period. There were CCI [redacted] participants with platelet count CCI [redacted]. There were no participants with platelet count CCI [redacted]. Clinically	**Monitoring & Stopping Criteria** **Laboratory Evaluations:** Platelet monitoring as presented in SoA tables. Monitoring and stopping criteria are presented in Section 7.1.5.

Signals or Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	significant bleeding events were not reported in clinical studies with bepirovirsen.	
Drug-induced kidney injury	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 CCI [redacted] Transient reductions in eGFR were seen in CCI [redacted] but no associated changes in other renal laboratory parameters or urinalysis have been identified. Fluctuation in eGFR was observed. The available data do not suggest that bepirovirsen is associated with renal injury.	**Monitoring & Stopping Criteria:** Monitoring of serum creatinine, estimated glomerular filtration rate (eGFR), urinalysis with microscopy and ACR will be performed as per the SoA tables (Section 10.2). Monitoring and Stopping criteria are presented in Section 7.1.7.

Signals or 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 erythema and injection site pruritis. Few events have led to treatment discontinuation.	**Monitoring & Mitigation:** Participants are assessed for ISRs at all visits during the treatment period. In order to minimize the risk of injection site reaction, bepirovirsen injections should be rotated within each anatomical site or site(s) of injection should be changed administration-to-administration. Injection into areas with ongoing injection site reactions should be avoided.
Study Procedures		
Sensory nerve conduction tests	Participant may experience mild discomfort at the time of the procedure	Although there is no evidence that NCS causes problems with these devices, participants with pacemakers or implantable automatic cardioverter-defibrillators will be excluded
Other		
COVID-19	Participation within an inpatient environment may increase risk of contracting COVID-19. Exposure to other participants and staff may increase risk of exposure.	COVID-19 tests are required at screen and on Day -1 (see SoA tables). Vaccination will be permitted during the study. Monitoring of clinical presentation of COVID-19 signs/symptoms. Conduct study at sites which have appropriate mitigation strategies in place.

2.3.2. Benefit Assessment

The first two parts of this study were conducted in healthy participants; no direct medical benefit was derived by their participation.

Part 3 will be conducted in PLWCHB on stable NA therapy with GSK3965193/Placebo CCI followed by CCI of bepirovirsen treatment. Participants may demonstrate a lowered HBsAg, but no durable medical benefit will be expected CCI GSK3965193 treatment period; however, participants will be making a valuable contribution to scientific knowledge of the treatment of CHB. Participants on stable NA therapy with HBsAg levels CCI at screen who opt to receive open label bepirovirsen after GSK3965193 treatment may experience a moderate rate of sustained HBsAg and HBV DNA loss 12% [Yuen, 2022].

Part 4 will study the safety and efficacy of GSK3965193 in combination with bepirovirsen CCI There is a need in patients with CHB for a finite treatment that allows them to achieve immune control of their infection (complete response, defined as HBsAg and HBV DNA below LLOQ for 6 consecutive months after the planned end of treatment), removing the need for lifelong therapy and to improve long term disease outcomes, particularly development of hepatocellular carcinoma.CCI

2.3.2.1. Overall Benefit: Risk Conclusion

The potential risks associated with GSK3965193 alone and in combination with bepirovirsen can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential participants is considered low.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with GSK3965193 alone and in combination with bepirovirsen are justified by the anticipated benefits that may be afforded by the future development of a new therapy for patients with CHB.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Objectives	Endpoints
Part 1 and Part 2 (healthy participants)	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Part 2)
• To evaluate the PK characteristics of single and repeat doses of GSK3965193	• Area under the plasma-concentration time curve (AUC): $AUC_{(0-\infty)}$ for single dose and $AUC_{(0-tau)}$ for repeat dose, maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (T1/2) will be calculated as data permits per part
Secondary	
• To investigate the effect of food on the PK characteristics of CCI [redacted] of GSK3965193	• Area under the plasma-concentration time curve (AUC): $AUC_{(0-\infty)}$, and maximum observed plasma drug concentration (Cmax) as data permits
Exploratory	
CCI [redacted]	

Objectives	**Endpoints**
• To investigate metabolites in plasma, urine and bile for GSK3965193	• Metabolite identification and concentration measurement in plasma, urine and bile (Part 2 only)
Part 3 and Part 4 (participants living with chronic hepatitis B infection [PLWCHB])	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193 monotherapy (Part 3) and in combination with bepirovirsen (Part 4)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, cardiac parameters (electrocardiogram), and sensory nerve conduction
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• Maximum reduction of serum HBsAg levels from baseline CCI [redacted]
• To evaluate efficacy of GSK3965193 in combination with bepirovirsen in PLWCHB (Part 4)	• Achieving complete response (undetectable serum HBV DNA and HBsAg for 6 consecutive months after the planned end of treatment of bepirovirsen)
Secondary	
• To evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB (Part 3)	• $AUC_{(0\text{-}tau)}$, Cmax, Tmax, and apparent terminal half-life (T1/2) will be calculated as data permits
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• ≥0.5x log IU/mL reduction of serum HBsAg levels from baseline anytime during the study (on-treatment and post-treatment)
• To assess the safety and tolerability of bepirovirsen monotherapy in PLWCHB who have completed GSK3965193/placebo monotherapy (Part 3)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis) and vital signs

Objectives	**Endpoints**
• To evaluate PD effect of GSK3965193 in combination with bepirovirsen in PLWCHB (Part 4)	• HBsAg loss (defined by two consecutive measurements of HBsAg below the limit of quantification) anytime during the study (on-treatment and post-treatment)
Exploratory	

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

Estimands

Treatment condition:

1. Part 1 and 2: Ascending single and multiple doses of GSK3965193 and Placebo
2. Part 3: GSK3965193 CCI [redacted] or Placebo
3. Part 4: Placebo in combination with bepirovirsen or GSK3965193 in combination with bepirovirsen CCI [redacted]

Population:

1. Part 1 and Part 2: Healthy participants
2. Part 3 and Part 4: PLWCHB treated on stable NA therapy

Table 1 Estimand framework for Safety for Part 1 and Part 2 in Heathy participants and Part 3 (GSK3965193 monotherapy) and Part 4 (combined with Bepirovirsen) in PLWCHB

Estimand Category	**Estimand**		
	Variable/Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
First Main Estimand Primary Objective 1: To assess the safety and tolerability of oral administration of GSK3965193	Incidence of AEs, SAEs, and AEs leading to withdrawal Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, and cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Parts 2, 3, 4)	Part 1: Single dose. No intercurrent event identified Part 2, 3 and 4: Intercurrent event of discontinuation of, interruption in, and non-adherence to GSK3965193 will be handled by treatment policy strategy, i.e., regardless of the intercurrent event occurring	Categorical variables: proportions Continuous variables: mean, standard deviation, median, minimum, and maximum
Second Main Estimand Secondary Objective 3 Part 3: To assess the safety and tolerability of bepirovirsen monotherapy in PLWCHB who have completed GSK3965193 monotherapy	Incidence of AEs, SAEs, and AEs leading to withdrawal Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, and cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Parts 2, 3, 4)	Intercurrent event of discontinuation of, interruption in, and non-adherence to GSK3965193 will be handled by treatment policy strategy, i.e., regardless of the intercurrent event occurring	Categorical variables: proportions Continuous variables: mean, standard deviation, median, minimum, and maximum

Table 2 Estimand framework for PD for Part 3 (GSK3965193 monotherapy) and Efficacy and PD for Part 4 (concurrently GSK3965193 with Bepirovirsen) in PLWCHB

Estimand Category	Estimand (Part 3 and Part 4)		
	Variable/Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary Objective 2: To evaluate PD effect of GSK3965193 monotherapy in PLWCHB (Part 3) First Main Estimand	• Maximum reduction of serum HBsAg levels from baseline CCI [redacted]	• Hypothetical strategy, discontinuation of, interruption in, and non-adherence to GSK3965193 related to or not related to any wide disruptive events will be handled assuming they had not happened (hypothetical strategy).	• Mean averaged over all PLWCHB in each treatment group
Primary Objective 3: To evaluate efficacy of GSK3965193 in combination with bepirovirsen (Part 4) Second Main Estimand	• Achieving complete response (undetectable serum HBV DNA and HBsAg for 6 months after the planned end of treatment of bepirovirsen)	• Intercurrent event of discontinuation of, interruption in, and non-adherence to GSK3965193 not related to any wide disruptive events and for change in the background NA therapy will be ignored (treatment policy strategy) • Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to bepirovirsen and GSK3965193 will be handled assuming they had not	• Proportion of PLWCHB

Estimand Category	Estimand (Part 3 and Part 4)		
	Variable/Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		happened (hypothetical strategy).	
Secondary Objective 1: To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3) Third Main Estimand	• ≥0.5 x log IU/mL reduction of serum HBsAg levels from baseline any time during the study (on-treatment and post-treatment)	• Same as Primary Objective 2 for Part 3	• Proportion of PLWCHB
Secondary Objective 2: To evaluate PD effect of GSK3965193 in combination with bepirovirsen (Part 4) Fourth Main Estimand	• HBsAg loss (defined by two consecutive measurements of HBsAg below the limit of quantification) anytime during the study (on-treatment and post-treatment)	• Same as Primary Objective 3 for Part 4	• Proportion of PLWCHB
First Supplementary Estimand	• Achieve complete response (undetectable serum HBV DNA and HBsAg ≥6 months after the actual end of treatment of bepirovirsen)	• Discontinuation of, interruption in, and adherence to GSK3965193 and bepirovirsen, will be accounted CCI [redacted]	• Proportion of PLWCHB

Estimand Category	Estimand (Part 3 and Part 4)		
	Variable/Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		• Wide disruptive events CCI [redacted]	
Second Supplementary Estimand	• The treatment duration of GSK3965193 and bepirovirsen received by participants before completion or discontinuation of each treatment	• Discontinuation of, interruption in, and adherence to GSK3965193 and bepirovirsen, will be accounted CCI [redacted] • Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3965193 and bepirovirsen will be handled with CCI [redacted]	• Mean treatment duration received by participants

4. STUDY DESIGN

4.1. Overall Design

This CCI [redacted] placebo-controlled study will assess the safety, tolerability, PK, and PD of GSK3965193 monotherapy in healthy participants; and GSK3965193 as monotherapy or concurrent combination with bepirovirsen in PLWCHB receiving stable NA therapy. The study design schematic is presented in Section 1.2. Study treatment and post-treatment follow-up Schedule of Activities (SoA) Tables are provided in Section 1.3.

4.2. Study Intervention Groups and Duration

4.2.1. Part 1

Part 1 CCI [redacted], dose escalation study in CCI [redacted] sequential cohorts of healthy participants that has completed. A sufficient number of healthy participants were screened CCI [redacted] Participants in each cohort were CCI [redacted] different dose levels) of GSK3965193 or matching placebo as an oral dose CCI [redacted] (defined here as 4 hours pre-dose and 2 hours post-dose) in 4 treatment periods shown in Table 3 and Table 4.

CCI [redacted]

CCI [redacted]

The initial dosing for all periods in which the dose level has been escalated was staggered so that CCI [redacted] were dosed as sentinel participants, one with study drug and one with placebo. After approximately 24 hours, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period were dosed. A review of safety, tolerability, and PK occurred prior to administration of the next oral dose level. This review occurred after at least 3 days of data collection CCI [redacted]. Participants returned for their next scheduled dosing period once at least 5 half-lives have elapsed and once all information for dose adjustment/ escalation has been received and reviewed, CCI [redacted]

The starting dose for Cohort 1 CCI [redacted] (refer to Section 4.5 for Dose Justification). The decision to proceed to the next oral dose level was made by the Dose Escalation Committee based on safety, tolerability and available PK data. Dose escalation did not exceed CCI [redacted].

Participants in Part 1 were enrolled in the study for CCI [redacted]

If a participant withdraws prematurely from Part 1 of the study, additional participants may be recruited and assigned to the same treatment sequence, starting from the current dosing period of the early withdrawal at the discretion of the sponsor in consultation with the investigator.

4.2.2. Part 2

Part 2 was composed of two sub-parts (Part 2A and Part 2B) and has completed.

4.2.2.1. Part 2A

Part 2A was a 14-day repeat oral dose, dose escalation study with CCI in CCI participants who were not enrolled in Part 1 of the study. A sufficient number of healthy participants was screened to ensure approximately CCI were randomized, with the aim to achieve CCI in each cohort. Participants were randomized CCI to receive either GSK3965193 CCI or placebo CCI under fasted conditions in each cohort. Each dose escalation cohort was staggered so that CCI were dosed as sentinel participants, CCI After at least CCI the investigator considered the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the cohort were dosed. The CCI however, this duration may be adjusted based on emerging PK data.

Part 2A started while Part 1 was still ongoing. The doses selected for Part 2 were based on CCI Part 1. The starting dose in Part 2 CCI (refer to Section 4.5 for Dose Justification). Dose escalation did not exceed 3.3-fold between doses. In addition, the predicted steady state systemic exposure in Part 2 did not exceed the predetermined systemic exposure stopping criteria. Participants CCI Timings of meals are detailed in the SoA (Section 1.3). The CCI dosing regimen and the timing of meals relative to dosing may be adjusted based on emerging PK data.

The actual doses administered in Part 2A were adjusted based on emerging safety, tolerability and PK data; these dose adjustments may involve either an increase or a decrease in the planned dose or to repeat a dose level. Sentinel dosing will not be required in a cohort should the dose be equivalent to, or lower than a dose already given in Part 2A. Preliminary safety and tolerability data from 14 days of dosing and PK data from 7 days of dosing for each cohort was reviewed prior to dose escalation and was used to determine the dose to be administered in the subsequent cohort. The decision to proceed to the next dose level was made by the Dose Escalation Committee based on safety, tolerability and available PK data.

The starting dose for Part 2A (Cohort 3) was CCI

Participants were enrolled in the study for approximately CCI

If a participant withdrew prematurely from Part 2A of the study, additional participant could be recruited and assigned to the same repeat dose level, starting from baseline at the discretion of the sponsor in consultation with the investigator.

4.2.2.2. Part 2B

Part 2B was CCI of healthy participants to evaluate the safety, tolerability and PK parameters of GSK3965193 CCI that has completed. A sufficient number of healthy participants were screened to ensure CCI described in Table 5, with the aim to achieve CCI periods shown in Table 5.

CCI

CCI
Participants returned CCI once all safety and tolerability CCI and PK data CCI from CCI has been received and reviewed, which is anticipated CCI after administration of the study drug in CCI This allowed for an appropriate PK washout period CCI between the periods. In CCI the CCI received GSK3965193 under fasted conditions in CCI under fed conditions, and vice versa. On the dosing day CCI During the reminder of the study, participants could receive standardized meals scheduled at the same time throughout the study for fasted and fed treatment periods.

The starting dose for Part 2B (Cohort 6) was CCI of GSK3965193. Sentinel dosing was not planned in Part 2B, as single doses up to exposures of CCI have been well-tolerated.

Participants in Part 2B were enrolled in the study for approximately CCI

If a participant withdrew prematurely from Part 2B of the study, additional participants could be recruited and assigned to the same treatment sequence, starting from the current dosing period of the early withdrawal at the discretion of the sponsor in consultation with the investigator.

4.2.3. Part 3

Part 3 is CCI [redacted] This part will commence after completion of both Part 1 and Part 2. A sufficient number of PLWCHB participants will be screened to CCI [redacted]

The GSK3965193 dose for Part 3 has been selected based on CCI [redacted]

After GSK3965193/Placebo dosing and 2 weeks of washout are completed, participants with screen HBsAg levels CCI [redacted] in this cohort will be offered the option to receive CCI [redacted] open label bepirovirsen CCI [redacted] The dose of bepirovirsen CCI [redacted]

Participants who opt to continue with bepirovirsen treatment will be enrolled for approximately CCI [redacted]
Participants who do not participate in bepirovirsen treatment will be followed up for 2 weeks off-treatment. These participants will be enrolled for approximately CCI [redacted]

If a participant withdraws prematurely from GSK3965193/Placebo monotherapy in Part 3 of the study, additional participants may be recruited at the discretion of the sponsor in consultation with the investigator. A participant who withdraws prematurely from optional bepirovirsen treatment in Part 3 will not be replaced.

Blinded safety data from Part 3 will be monitored by the safety review team (SRT). Unblinded safety and PD data in Part 3 (only on participants who opt to receive bepirovirsen and once all have completed treatment) will be reviewed by the Independent Data Monitoring Committee (IDMC) that has been overseeing bepirovirsen studies.

4.2.4. Part 4

Part 4 is CCI with CCI level of GSK3965193 or placebo in combination with bepirovirsen in CCI of PLWCHB on stable NA therapy who have not participated in Part 3 of the study. This part will commence after completion of Part 3, contingent on the clinical safety and efficacy data from Part 3. A sufficient number of PLWCHB participants will be screened to ensure at CCI participants are randomized, with the aim to achieve CCI completed in the cohort. Participants will be CCI to receive either GSK3965193 CCI or placebo CCI All participants in this cohort will also receive open-label bepirovirsen CCI

The dose of GSK3965193 for Part 4 is expected to be CCI

The dose of bepirovirsen corresponds CCI . The predicted steady state systemic exposures of GSK3965193 and bepirovirsen in Part 4 will not exceed the predetermined systemic exposure stopping criteria. Participants will receive both GSK3965193 and bepirovirsen CCI ; after 28 days, bepirovirsen dosing will continue CCI

Participants will be enrolled for approximately CCI and approximately CCI

If a participant withdraws prematurely from Part 4 of the study, additional participants may be recruited at the discretion of the sponsor in consultation with the investigator.

Blinded safety data from Part 4 will be monitored by the safety review team (SRT). Unblinded safety and efficacy data in Part 4 will be monitored by an Independent Data Monitoring Committee (IDMC). A separate charter will be established for the IDMC.

4.3. Number of Participants

The planned number of evaluable participants will be CCI and allocated as follows.

Part 1: CCI
Part 2:
Part 3:
Part 4:

In the case of a disruptive event (e.g., COVID-19, natural disaster), sites and/or participants may be unable to conduct/attend dosing visits, conduct/attend follow-up visits, participants may be discontinued from study treatment, and/or participants may be withdrawn from the study.

4.4. Scientific Rationale for Study Design

This study design is based on well-established and published methods to evaluate the first single and repeat dose administration of experimental drugs including the use of sentinel dosing. This study includes a placebo arm to allow for a valid evaluation of adverse events attributable to treatment versus those independent of treatment.

CCI

[redacted]

CCI [redacted]

[redacted]

4.4.1. Rationale for Peripheral Neuropathy Monitoring

CCI [redacted]

[redacted]

4.4.2. Rationale for EnteroTracker and Urine Collection

CCI [redacted]

CCI [redacted]

[redacted]

4.4.3. Participant Input into Design

CCI [redacted]

[redacted]

[redacted]

[redacted]

4.5. Justification for Dose

4.5.1. Human Pharmacokinetics Prediction

CCI [redacted]

CCI [redacted]

4.5.2. Preclinical Pharmacology and Safety Margins

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.5.3. Starting Dose Rationale (Part 1)

CCI [redacted]

CCI [redacted]

4.5.4. Therapeutic Dose Rationale

Estimates of concentration at the end of a dosing interval at steady state (Cmin) from the PBPK model were combined with potency data from the CCI [redacted] described above to estimate the therapeutic dose.

CCI [redacted]

4.5.5. Maximum Dose Rationale

The maximum single dose in Part 1 is defined based on the following:

CCI [redacted]

CCI [redacted]

4.5.6. Planned Doses and Safety Coverage (Parts 1 and 2ia)

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.5.7. Planned Tablet Dose and Safety Coverage (Parts 3 and 4)

CCI [redacted]

CCI

[redacted]

4.5.8. Dose Levels, Frequency and Duration of Bepirovirsen

CCI [redacted]

[redacted]

4.5.9. Co-administration and Drug-drug Interactions

No drug-drug interactions affecting the PK for the co-administration of GSK3965193 and bepirovirsen or nucleos(t)ide analogues are expected CCI [redacted]

4.5.9.1. Co-administration of GSK3965193 with Bepirovirsen

CCI [redacted]

[redacted]

4.5.9.2. Co-administration of GSK3965193 with nucleos(t)ide analogues

CCI [redacted]

CCI [redacted]

4.5.9.3. Co-administration of bepirovirsen with nucleos(t)ide analogues

CCI [redacted]

4.6. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study at follow-up (last subject last visit) shown in the Schedule of Activities for the last participant globally.

A participant is considered to have completed the study if he/she has completed all appropriate study visits including the last scheduled procedure shown in the Schedule of Activities.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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. Inclusion Criteria for Healthy Participants and PLWCHB

AGE
1. **Parts 1 and 2**: between 18 and 55 years of age inclusive, at the time of signing the informed consent. **Parts 3 and 4**: between 18 (or local legal age of consent) and 65 years of age inclusive, at the time of signing the informed consent
WEIGHT
2. Body weight ≥50 kg and body mass index within the range 18-32 kg/m^2 (inclusive)
SEX
3. Male or female participant: a. A male participant is eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study treatment (GSK3965193) in Parts 1, 2 and 3 and at least 90 days after the last dose of bepirovirsen in Part 4 or the optional Part 3 extension: i. Refrain from donating sperm AND ii. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent OR Must agree to use contraception/barrier as detailed below: Agree to use a male condom [and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak] when having sexual intercourse with a woman of childbearing potential who is not currently pregnant b. A female participant is eligible to participate: i. **Parts 1 and 2**: she is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 (Appendix 4)

ii. **Parts 3 and 4**: she is not pregnant or breastfeeding AND at least 1 of the following conditions applies:

1. Is a WONCBP as defined in Section 10.4 (Appendix 4), OR
2. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year) as described in Section 10.4.2, preferably with low user dependency during the intervention period and for at least 7 days after the last dose of study treatment in Part 3 and 90 days after the last dose of bepirovirsen in Part 4 or if the participant chooses to continue with the optional bepirovirsen extension in Part 3. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
3. A WOCBP must have a negative highly sensitive pregnancy test (serum) at screening and on Day -1, see Section 8.2.8 (Pregnancy Testing).

– Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.8.

– 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.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

INFORMED CONSENT

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

5.1.2. Additional Inclusion Criteria for Healthy Participants (Parts 1 and 2)

TYPE OF PARTICIPANT

5. Participants who are healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring

5.1.3. Additional Inclusion Criteria for PLWCHB (Parts 3 and 4)

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
6. Participants who have documented chronic HBV infection ≥6 months prior to screening
7. Participants currently receiving stable nucleos(t)ide analog (NA) therapy (e.g., tenofovir disoproxil, tenofovir alafenamide, entecavir). "Stable" is defined as no changes to the nucleos(t)ide regimen for at least 6 months prior to screening and with no planned changes to the regimen for the duration of the study
8. Plasma or serum HBsAg concentration >100 IU/mL
9. Plasma or serum HBV DNA concentration <90 IU/mL
10. HBeAg positive or negative
11. ALT ≤2 x the upper limit of normal (ULN)

5.2. Exclusion Criteria

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

5.2.1. Exclusion Criteria for Healthy Participants

MEDICAL CONDITIONS
1. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study
2. A current diagnosis of migraine headache
3. Positive Hepatitis A virus antibody (HAV Ab (IgM), or positive for HBV, hepatitis C virus (HCV) or human immunodeficiency virus (HIV) at screening
4. ALT >1 x ULN
5. Bilirubin >1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones)
7. Corrected QT interval (QTc) >450 msec **NOTE**: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an

MEDICAL CONDITIONS
individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
8. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome. Any significant arrhythmia which, in the opinion of the Investigator or GSK Medical monitor (if required), will interfere with the safety for the individual participant.
9. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).
10. Signs and symptoms suggestive of COVID-19. **NOTE**: Assessments will be performed in accordance with local site procedure.
11. For participants in Part 2A only: i. Personal history or family history of peripheral neuropathy ii. A score ≥4 on the Toronto Clinical Scoring System for Polyneuropathy
PRIOR/CONCOMITANT THERAPY AND CLINICAL STUDY EXPERIENCE
12. Past or intended use of over-the-counter or prescription medication, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days before the first dose of study intervention, unless in the opinion of the Investigator, the medication will not interfere with the study procedures or compromise participant safety. **NOTE**: Use of paracetamol or acetaminophen, at doses ≤2 g/day and/or use of simple analgesics is acceptable
13. Recent donation of blood or blood products such that participation in the study would result in loss of blood in excess of 500 mL within 56 days
14. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
15. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day
16. Unwillingness or inability to follow the procedures outlined in the protocol or any other type of medical research within 30 days of randomization

DIAGNOSTIC ASSESSMENTS
17. Positive pre-study drug/alcohol screen 18. Positive test for COVID-19 infection **NOTE**: Assessments will be performed in accordance with local site procedure

OTHER EXCLUSIONS
19. Current or history of drug abuse 20. Regular alcohol consumption within 6 months prior to the study defined as: An average weekly intake of > 14 units for both males and 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 21. Current or previous use of tobacco- or nicotine-containing products (e.g., cigarettes, nicotine patches or electronic devices) within 6 months before screening and/or have a smoking pack history of > 5 pack years **NOTE**: 1 pack year = 20 cigarettes per day for 1 year or 5 cigarettes per day for 4 years 22. Positive breath carbon monoxide test indicative of recent smoking at screening or each in-house admission to the clinical research unit 23. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicates participation in the study

5.2.2. Exclusion Criteria for PLWCHB

MEDICAL CONDITIONS
24. Clinically significant abnormalities affecting physical or mental health in medical history or on physical examination (e.g., moderate-severe liver disease other than chronic HBV, acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening, significant/unstable cardiac disease (including pacemaker or AICD), uncontrolled diabetes, bleeding diathesis or coagulopathy), apart from chronic HBV infection. 25. Co-infection with: a. Current or past history of HCV b. HIV c. Hepatitis D virus (HDV)

26. History of or suspected liver cirrhosis and/or evidence of cirrhosis as determined by:
    a. both aspartate aminotransferase (AST)-Platelet Index (APRI) >2 and FibroSure/FibroTest result >0.7
    b. Regardless of APRI or Fibrosure/FibroTest score, if the participant meets 1 of the following criteria, they will be excluded from the study
        i. Liver biopsy-based diagnosis of cirrhosis (e.g. Metavir Fibrosis Grade F4)
        ii. Liver stiffness >12 kPa
27. Diagnosed or suspected hepatocellular carcinoma as evidenced by the following:
    a. Alpha-fetoprotein concentration ≥200 ng/mL
    b. If the screening alpha-fetoprotein concentration is ≥50 ng/mL and <200 ng/mL, the absence of liver mass must be documented by imaging within 6 months before randomization
28. History of malignancy within the past 5 years with the exception of specific cancers that are cured by surgical resection (e.g., skin cancer). Participants under evaluation for possible malignancy are not eligible
29. 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] or history/presence of other diseases that may be associated with vasculitis condition (e.g., systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, mononeuritis multiplex)
30. History of extrahepatic disorders possibly related to HBV immune conditions (e.g., nephrotic syndrome, any type of glomerulonephritis, polyarteritis nodosa, cryoglobulinaemia, uncontrolled hypertension)
31. History of alcohol or drug abuse/dependence
    a. Current alcohol use as judged by investigator to potentially interfere with participant compliance
    b. History of or current drug abuse/dependence as judged by the investigator to potentially interfere with participant compliance

    NOTE: Refers to illicit drugs and substances with abuse potential. Medications that are used by the participant as directed, whether over-the-counter or through prescription, are acceptable and would not meet the exclusion criteria
32. History of or other evidence of bleeding from esophageal varices
33. Documented history or other evidence of metabolic liver disease within 1 year of randomization
34. Documented history or other evidence of diabetes (regardless of insulin-dependence)

MEDICAL CONDITIONS
35. Personal history or family history of peripheral neuropathy 36. A score >4 on the Toronto Clinical Scoring System for Polyneuropathy 37. History of having received or currently receiving any systemic anti-neoplastic (including radiation) or immune-modulatory treatment (including systemic oral corticosteroids) within the 3 months prior to randomization or the expectation that such treatment will be needed at any time during the study 38. Currently taking, or has taken within 12 months of randomization, any interferon-containing therapy. 39. Abnormal and clinically significant 12-lead ECG finding. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the study. An abnormal and clinically significant finding that would preclude a participant from entering the study is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following: a. Atrial fibrillation (AF) with rapid ventricular rate >120 bpm b. sustained or non-sustained ventricular tachycardia c. second degree heart block Mobitz type II and third-degree heart block d. QTcF >450 msec

PRIOR/CONCOMITANT THERAPY AND CLINICAL STUDY EXPERIENCE
40. Currently taking, or taken within 3 months prior to randomisation, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks) or topical/inhaled steroid use 41. Participants for whom immunosuppressive treatment is not advised, including therapeutic doses of steroids, will be excluded 42. Participants requiring anti-coagulation therapies (for example warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel or aspirin) 43. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives (if known) or twice the duration (if known) of the biological effect of the study treatment (whichever is longer) or 90 days (if half-life or duration is unknown) 44. Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing day. Patients who have received a course of bepirovirsen, even if it has been more than 12 months, are excluded.
DIAGNOSTIC ASSESSMENTS
45. Positive test for COVID-19 infection **NOTE**: Testing must be performed. Method of testing will be in accordance with local site procedure.

46. Laboratory results as follows:

    a. Serum albumin ≤3.5 g/dL
    b. Glomerular filtration rate (GFR) ≤60 mL/min /1.73m^2 as calculated by the chronic kidney diseases epidemiology collaboration (2021 CKD-EPI) formula
    c. INR >1.25
    d. Platelet count <140 X 10^9 /L
    e. Total bilirubin >1.25 x ULN
    f. Urine ACR ≥0.03 mg/mg (or ≥30 mg/g). In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement.

    NOTE: In cases where participants have low urine albumin and low urine creatinine levels resulting in a urine ACR calculation ≥0.03 mg/mg, the investigator should confirm that the participant does not have a history of diabetes, hypertension or other risk factors that may affect renal function.

OTHER EXCLUSIONS

47. Regular alcohol consumption within 6 months prior to the study defined as:

    An average weekly intake of > 14 units for both males and 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

48. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicates participation in the study

49. Participants with a fear of needles

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, or grapefruit hybrids from 7 days before the start of GSK3965193 treatment until after the final dose.

CCI [redacted]

5.3.2. Caffeine, Alcohol, and Tobacco

Inpatient

Parts 1 and 2 only: During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or

pharmacodynamic sample. Other decaffeinated drinks will be permitted except during fasting periods where these are required in Part 2.

Alcohol consumption and use of tobacco products are not permitted in the clinical unit.

Outpatient

During each visit, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. For the duration of the study, until final follow-up, participants are encouraged to refrain from changing their activity beyond that which they normally perform. Additionally, participants will abstain from taking creatine-containing exercise supplements for all parts of the study.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Individuals who fall out of the screening window, may be rescreened at the discretion of the investigator and site. Individuals who do not meet the criteria for participation only due to COVID-19 infections may also be rescreened after recovery. Rescreened participants should be assigned a new participant identifier for every screening/rescreening event. Previously assigned participant identifier(s) are to be recorded in participants' eCRF.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Not Applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational product(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. An investigational product is defined as pharmaceutical form of an active substance. A placebo is defined as an inactive substance that looks the same as, and is given in the same way as, the investigational product being studied. No non-GSK comparators are used in this study. CCI [redacted]

6.1. Study Intervention(s) Administered

The following products will be received by the participant as per the protocol design.

Parts 1 and 2A - CCI [redacted]

Part 2B - CCI [redacted]

Part 3 - CCI [redacted]

Part 4 - CCI [redacted]

CCI [redacted]

CCI [redacted]

The site of injection of bepirovirsen will be recorded for each participant and dose(s). Sites of injection are listed in order of preference and are a guide for the clinical staff.

CCI [redacted]

Injections should be rotated within each anatomical site or site(s) of injection should be changed administration-to-administration. Injection into areas with ongoing injection site reactions should be avoided.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions 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 or administer study intervention. All study interventions 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, or the head of the medical institution (where applicable) 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 intervention 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 study monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using a Randomisation and Trial Supply Management System (RTMS). Before the study is initiated, the log in information and directions for the RTMS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

On Day 1 of the first dosing for each cohort, participants will be assigned a unique randomisation number in ascending numerical order. The randomisation number encodes the participant's assignment to either GSK3965193 or placebo, according to the randomisation schedules generated prior to the study by the Statistics Department at GSK, using validated internal software. The Principal Investigator (PI) or delegated responsible person will assign the randomisation numbers as described above and the randomisation number will be entered in the case report form (CRF). In Part 4, all participants will receive bepirovirsen in addition to the randomised treatment.

This study (Parts 1, 2A, 3 and 4) is double blind with participants and the site staff blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, in Parts 1 and 2 an unblinded pharmacist will be responsible for the reconstitution and dispensing of all study intervention; in Parts 3 and 4 all site staff will be blinded. Once a treatment period in Part 1 or a cohort in Part 2A has completed, selected members of the sponsor staff were unblinded to the treatment allocations of participants who completed the treatment to enable the analysis and modelling of PK data to start the next period or cohort. The GSK/clinical research organization personnel did not have access to participant-specific treatment assignment to avoid potentially introducing bias in discussion with the study site. In Part 1 and Part 2A, the pharmacokineticists, statisticians and programmers, however, needed access to participant randomization during the course of the single dose escalation and repeat dose escalation parts of the study for analysis purposes to support dose adjustments and escalations. Other GSK staff may be included in discussions around dose adjustments and progression if it is deemed necessary and relevant by the above-mentioned GSK study team members. Part 2B is open label. The Sponsor will present data at Dose Escalation Committee (DEC) and Safety Review Team (SRT) meetings in a blinded fashion when interacting with site staff.

Treatment sensitive lab data have been identified and include PK data, exploratory HBV biomarker data and in-stream HBsAg and HBV DNA results. CCI [redacted]

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

A participant will be withdrawn if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one 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.

GSK staff analysing samples derived from this study will be unblinded. Drug concentration information that may unblind the study will only be shared with the DMPK Study Director and scientists who are conducting and reporting the GSK3965193 metabolism study which is separate from this protocol. This information is needed to differentiate active-dosed participants from placebo to inform on the metabolite

identification study conduct. Drug concentration information will not be reported to investigative sites or blinded personnel until the study has been unblinded.

6.4. Study Intervention Compliance

When participants are dosed at the site, 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. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

When participants self-administer GSK3965193 or placebo at home, compliance with GSK3965193 or placebo CCI [redacted] during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of GSK3965193 or placebo CCI [redacted] dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

GSK3965193

Dose justification and stopping criteria are detailed in Section 4.5 and Section 7.1, respectively.

CCI [redacted]

Bepirovirsen

Dose modifications are not planned for this study.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment with either GSK3965193 or bepirovirsen after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of GSK3965193 CCI [redacted] or bepirovirsen greater than CCI [redacted] within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat an overdose.

In the event of an overdose, the investigator or treating physician should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities for at least 4 days.

3. Obtain a plasma sample for PK analysis immediately unless a PK sample has already been obtained after the overdose.

4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment 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

CCI [redacted]

In Parts 3 and 4 nucleos(t)ide analogs taken by participants for CHB treatment and oral contraceptives as detailed in Section 10.4 are permitted. Participants must abstain from taking prescription or non-prescription 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 GSK3965193 until 14 days after the last dose, unless, in the opinion of the investigator, the medication will not interfere with the study. CCI [redacted]

CCI [redacted]

Traditional Chinese medicine and/or acupuncture as it relates to CHB therapy should be avoided during the duration of the study. If participants report use of traditional Chinese medicine and/or acupuncture, then details must be recorded in the concomitant medication CRF.

6.8.1. Nucleos(t)ide Treatment during and after the End of the Study (Parts 3 and 4)

The investigator is responsible for ensuring that consideration has been given to the care of the participant's medical condition, and that participants are able to continue their NA therapy over the duration of the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

6.8.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications are not permitted during the study.

- PEG-interferon or other immunomodulating therapies
- Immunosuppressing drug (e.g., prednisone) use >2 weeks duration from 3 months prior to randomization through to the final Follow-up visit (see Section 5.2)
- Prior treatment with any oligonucleotide or siRNA within 12 months prior to the first dosing
- Creatine-containing gym supplements
- Hepatitis B virus vaccinations
- Regular use of anti-coagulation therapies (e.g., warfarin, Factor Xa inhibitors or anti platelet agents like clopidogrel) or regular use of aspirin during bepirovirsen treatment

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

In rare instances, it may be necessary for a participant to permanently discontinue study treatment. A participant may discontinue study treatment at any time at his/her own request. Additionally, study treatment may be withdrawn at any time at the discretion of the Investigator for safety, behavioural or administrative reasons.

If study treatment is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy assessments. If a participant discontinues study treatment, an early discontinuation (ED) visit should be performed. See the SoA for data to be collected at the time of discontinuation of study treatment.

Following the ED visit the participant will enter the follow-up/post-treatment period following the visit schedule and required assessments that need to be completed, per the SoA.

In Part 3 of the study participants who discontinue study treatment during the GSK3965193 (or placebo) monotherapy phase should complete an ED visit and enter the two-week CCI [redacted] follow-up/washout period. If the participant CCI [redacted] and consented to optional bepirovirsen, progression into the optional bepirovirsen treatment period must not occur unless this has been discussed and agreed with the Medical Monitor prior to the day 43 visit.

If the patient withdraws consent to participate in the study completely the procedure described in Section 7.2 should be followed.

Stopping criteria, including their evaluation and confirmation, are detailed in Section 7.1.1 to Section 7.1.7. Participants meeting these criteria should be monitored until laboratory abnormalities resolve, stabilize, or return to within baseline values as indicated. This may be done at follow-up visits specified in the SoA or require additional visits to be scheduled.

Study treatment may be discontinued, and the participant potentially withdrawn from the study, if:

- A participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator, is possibly, probably or definitely related to investigational product.
- The participant initiates treatment with any prohibited medications.
- Individual or study level stopping criteria are met
- Deviation(s) from the protocol
- Withdrawal of consent by participant (or proxy)
- Discretion of the Investigator

- Participant is lost to follow-up
- Closure or termination of the study

In the event of any of the following, ongoing dosing will be halted for all participants in a dose group/cohort:

- Two or more participants in the same dose group/cohort experience non-serious severe AEs considered at least possibly related to the administration of GSK3965193. These two AEs do not need to be within the same system, organ, or class.
- Any participant experiences an SAE considered at least possibly related to the administration of GSK3965193.The dosing will be temporarily halted, and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the GSK medical monitor, relevant GSK personnel, and with the CA and Institutional Review Board (IRB)/Independent Ethics Committees (IEC) will then take place prior to any resumption of dosing, which may also include the evaluation of lower doses. If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the Regulatory Agencies and ethic committees. The trial will not restart until the amendment has been approved by the Agency(s) and ethic committee(s).

7.1.1. Liver Chemistry Monitoring and Stopping Criteria

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

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Part 3 (GSK3965193 Monotherapy)

Study intervention will be discontinued for a participant if liver chemistry stopping criteria in Figure 3 are met.

CCI

Refer to Section 10.6 for required liver safety actions, monitoring and follow-up to assess causality of liver event. Participants who do not meet protocol-specified liver event stopping criteria but met protocol-defined increased monitoring criteria may continue study intervention with liver chemistry monitoring at least weekly. Monitoring may take place at visits scheduled in the SoA, or additional visits as needed.

Part 3 (Bepirovirsen Monotherapy) and Part 4

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

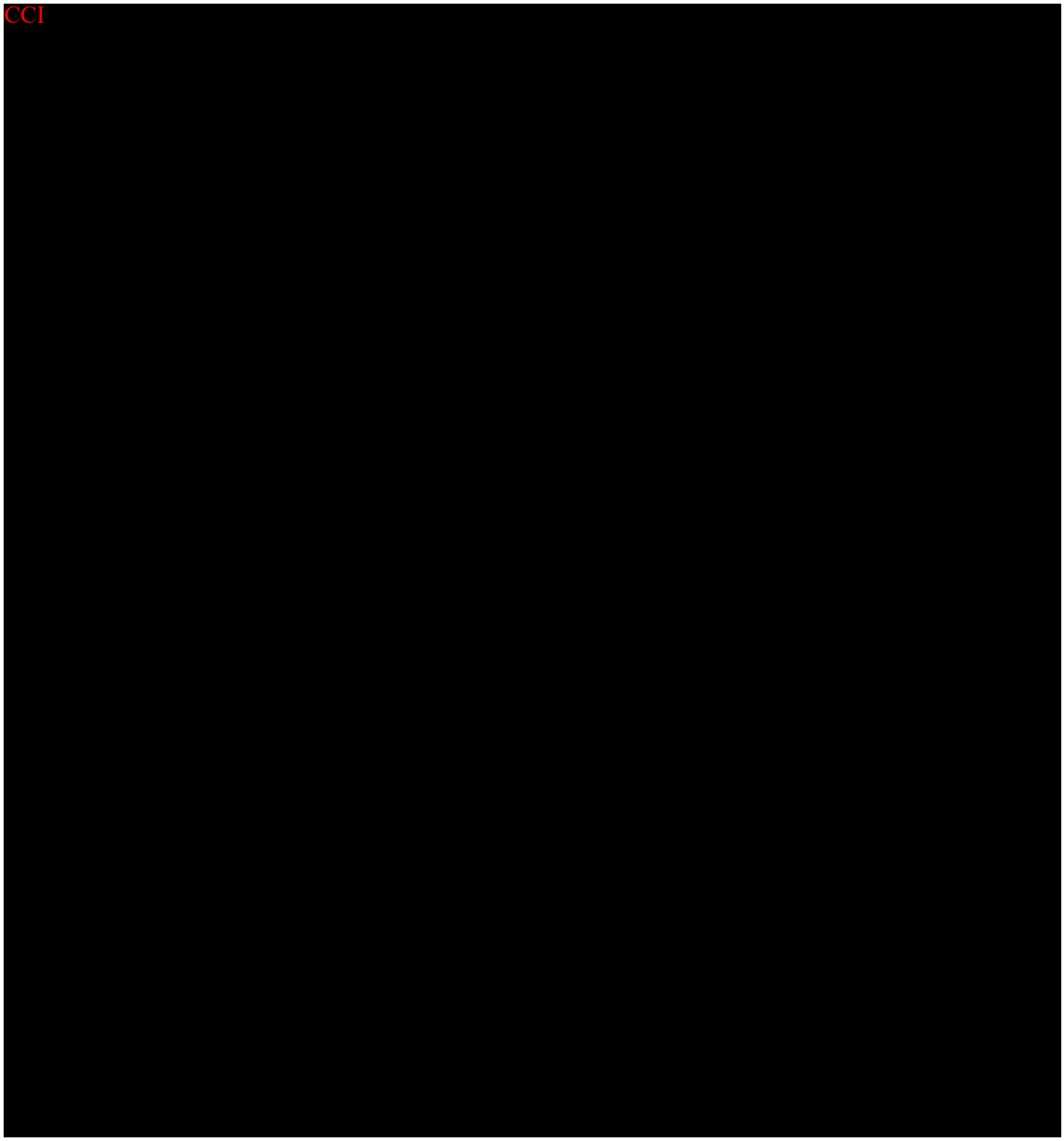
Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Table 8 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Table 8 lists the criteria for withholding or discontinuing the study medication in a study participant with elevation of ALT. Additional testing will be performed (see safety follow-up procedures for participants who meet increased monitoring or stopping criteria) and the participant monitored until liver chemistry abnormalities resolve, stabilize, or return to within baseline values.

If any of the criteria in Table 8 are met every attempt must be made to have the participant evaluated (as soon as possible; preferably within 24 hours) for repeat assessment of liver chemistries and additional testing and close monitoring (a specialist or hepatology consultation is recommended). Participants must be monitored twice weekly until liver chemistry abnormalities (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize, or return to within baseline values. Monitoring blood tests can be performed at scheduled visits in the SoA though additional unscheduled visits may be required depending upon the frequency of monitoring required. If study treatment is discontinued then an early discontinuation visit should be conducted and the participant will enter into the follow-up visit schedule as described in Section 7.1.

Table 8 Part 3 (Bepirovirsen Monotherapy) and Part 4 liver chemistry monitoring and stopping criteria

CCI



Notes:

- Any abnormal laboratory parameters that meet the criteria for individual treatment discontinuation must be confirmed by retest of a new collection of blood samples as soon as possible.
- Deterioration considered clinically significant from the baseline liver parameters must be confirmed by retesting ALT, total bilirubin, direct bilirubin, and INR (if available).
- As a reminder for investigators/sites, if local laboratory assessments are used for decision-making, collect central labs in parallel and record local results in the CRF.
- If one criterion in the list above is met and confirmed by retesting, further treatment may be discontinued for this participant. Results of retesting must be evaluated before the next dose is administered.
- Monitor participant until liver chemistry abnormalities resolve, stabilize, or return to within baseline values.
- Cases such as Gilbert syndrome, where baseline bilirubin values are high, should be discussed with the Medical Monitor, to assess if it is a case of DILI or the participant may continue with dosing.

The procedures listed below are to be followed if a participant meets any of the liver event criteria defined in Table 8.

- Notify the Medical Monitor within 24 hours of learning of the abnormality to confirm the participant's study treatment cessation and follow-up.
- Complete the Liver Event CRF.
- Complete the "Safety Follow-up Procedures" listed below.

Safety Follow-up Procedures for Participants Who Meet Any of The Liver Monitoring and Stopping Criteria:

Viral hepatitis serology including:

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

Obtain a blood sample for PK analysis as soon as possible following the occurrence of an event. Record the date/time of the PK blood sample collection and the date/time of the last dose of study treatment prior to blood sample collection on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. Instructions for sample handling and shipping are included in the Laboratory Manual.

Review INR.

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

Review fractionated bilirubin, if total bilirubin ≥ 1.5 X ULN

Assess eosinophilia.

Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the AE CRF.

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

Record alcohol use on the Liver Events CRF.

The following are **required for participants who meet the ALT and bilirubin stopping criteria** but are optional for other abnormal liver chemistries.

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

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified including, but not limited to changes from baseline in QTcF after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

The QTcF correction formula must be used for each participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. If an ECG demonstrates a prolonged QT interval, two more ECGs should be obtained over 5-10 mins and the average QTcF value of the three ECGs should be used to determine if the participant meets the QTc stopping criteria below.

A participant who meets the below QTc stopping criteria (based on the average of triplicate ECG readings) will be withdrawn from study intervention:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from baseline QTcF >60 msec

7.1.3. Pharmacokinetic Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule. The following stopping criteria will apply.

CCI

CCI

[redacted]

7.1.4. Neurologic Stopping Criteria

CCI

[redacted]

If 2 or more participants in the same dose group/cohort experience neurocognitive symptoms (DAIDS Altered Mental Status Grade 2) possibly related to study medication, the study will be halted and an SRT will be convened to review the data. In addition, the regulatory agency will be notified. The study will only be re-started after regulatory authority approval.

7.1.5. Haematological Stopping Criteria (Part 3 Bepirovirsen Monotherapy and Part 4 only)

During Part 3 bepirovirsen monotherapy and Part 4, if a participant develops signs or symptoms of thrombocytopenia, obtain a platelet count (local lab) as soon as possible and hold dosing until the platelet count is confirmed. If the platelet count is uninterpretable or below lower limit of normal (LLN) reference range, re-check the platelet counts as soon as possible. Samples showing platelet clumping should also be repeated.

Participants with platelet values CCI [redacted] will undergo further assessment

including, but not necessarily limited to, anti-platelet antibodies. If the participant has a positive anti-platelet antibody, study treatment should be discontinued, including bepirovirsen, permanently. Monitor until platelet abnormalities resolve, stabilize, or return to within baseline values.

Table 9 Haematological Stopping Criteria

CCI [redacted]

CCI

[redacted]

7.1.6. Drug Induced Vascular Injury (DIVI) and Complement Stopping Criteria (Part 3 Bepirovirsen Monotherapy and Part 4 only)

Treatment Hold

CCI

[redacted]

CCI [redacted]

Treatment Discontinuation

CCI [redacted]

7.1.7. Drug Induced Kidney Injury (Renal) Stopping Criteria (Part 3 Bepirovirsen Monotherapy and Part 4 only)

During Part 3 bepirovirsen monotherapy and Part 4, if any of the following are observed, results should be confirmed, and if confirmed, further evaluation for alternative causes should be pursued and discussed with the Medical Monitor:

CCI [redacted]

Bepirovirsen Treatment Hold/Treatment Discontinuation

CCI [redacted]

CCI [redacted]

7.1.8. Temporary Discontinuation

Not applicable for Parts 1 and 2B.

For Part 2A, 3 and 4, if a participant stops study treatment because he/she develops symptoms suggestive of Covid-19, the participant may restart study treatment at the discretion of the investigator if all the following criteria are met:

1. a negative Covid-19 test
2. dosing has been halted for no more than 48 hours
3. a minimum of 7 days remains in the study treatment period once dosing recommences

For Part 4, if a participant experiences a clinically significant AE that the investigator believes may be possibly, probably, or definitely related to investigational product and could potentially be exacerbated by the next dose, the investigator may delay investigational product dosing by withholding 1 dose and should contact the Medical Monitor.

7.1.9. Study Intervention Restart or Rechallenge after Stopping Criteria Met

If any stopping criteria are met by any participant in this study, study treatment restart or rechallenge is not allowed.

CCI [redacted]

CCI

[redacted]

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Management of Participants who Develop COVID-19 Symptoms During the Study

If a participant develops COVID-19 like symptoms during the study the following actions should be taken:

- During Part 1 or Part 2B, participants who develop signs/symptoms highly suggestive of COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures. Participants who develop symptoms suspicious of COVID-19 during washout periods should inform the site immediately.
- During Parts 2A, 3 and 4, study treatment should be halted for any participants who develop signs/symptoms highly suggestive of COVID-19 disease; they should be isolated and tested for COVID-19 in accordance with site procedures.
- In all cases, assessments should be continued as per the protocol where possible. Participants with a confirmed COVID-19 test may continue to complete safety monitoring assessments but will receive no further doses of the study treatment. In other cases, withdrawal of participants from the study will be at the discretion of the Principal Investigator
- Refer to Appendix 7 for further COVID-19 related study management details.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1 (Appendix 1).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed CCI
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Demographic data will be recorded 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. The year of birth is collected to stratify the population and determine the impact of the study intervention by age.

8.1. Efficacy Assessments

Applicable to Part 4 Only: The primary efficacy endpoint is sustained virologic response, which is a composite endpoint defined as HBsAg <LLOQ and HBV DNA <LLOQ at the end of bepirovirsen treatment which is sustained for 24 weeks post-bepirovirsen treatment. Seroclearance refers to participants with HBsAg and HBV DNA <LLOQ (with or without the formation of HBs-antibody). Seroconversion refers to participants with HBsAg and HBV DNA <LLOQ plus formation of HBs-antibody. Both terms are used to evaluate efficacy. For the purposes of this study, sustained response is defined as a continuous 6 months from end of planned bepirovirsen treatment during which levels of HBsAg in serum remain less than LLOQ and HBV DNA less than LLOQ.

Any HBsAg greater than LLOQ or HBV DNA greater than LLOQ after achieving HBsAg seroclearance and HBV DNA suppression needs to be confirmed by re-test within 1 week of receiving the test result. The re-test result will be used if the first test is not confirmed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the Skin, Respiratory (lungs only), Cardiovascular, Gastrointestinal (palpate abdomen, liver and spleen) and Neurological (lower limbs only) systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Pulse rate, respiratory rate and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse 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). Three readings of blood pressure and pulse will be taken at screening and pre-dose day 1 only. On Screening and day 1 pre-dose triplicate vitals will consist of 3 pulse and 3 blood pressure measurements at intervals of at least 1 min. Single measurements will be taken for all other timepoints.
- In Parts 3 and 4 vital signs assessments will include temperature measurement. Only a single temperature measurement is required.

8.2.3. Electrocardiograms

8.2.3.1. 12-Lead Safety ECGs

- Safety ECGs will be performed in semi-supine position after at least 5 minutes rest and printed and interpreted on-site by the Investigator to ensure participant safety.
- Triplicate OR Single 12-lead ECG 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 QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, the ECGs will be obtained at least 2 minutes apart and over a recording period of up to 10 minutes.
- Baseline QTcF will be based on the average of 3 pre-dose ECGs collected on Day 1 (in Part 1, Day 1 pre-dose for each treatment period should be considered as baseline).
- Refer to Section 7.1.2 for QTc specific stopping criteria.

8.2.3.2. Telemetry

- In addition to 12-lead safety ECGs, participants will be monitored on telemetry for each treatment period in Part 1 and for the first dose in Part 2A.

8.2.3.3. Continuous Cardiac Monitoring

- The continuous cardiac monitoring assessments will be based on ECGs extracted from Holter recordings.

- The continuous 12-lead digital ECG data will be stored onto SD memory cards. In case the cardiodynamic evaluation is undertaken, 12-lead ECGs will be extracted in replicates from the continuous ECG recording at pre-determined time points as defined in the SoA and will be read centrally.
- If a decision is taken to undertake cardiodynamic evaluations, details will be outlined in a separate analysis plan. The following principles will be followed in a core laboratory if TQT analysis is requested:
  - ECG analysts are blinded to the participant, visit and treatment allocation.
  - Baseline and on-treatment ECGs for a particular participant will be overread on the same lead and will be analysed by the same reader.
  - The primary analysis lead is lead II. If lead II is not analysable in any specific participants, then primary lead of analysis will be changed to another lead for the entire participant data set.

8.2.4. Sensory Nerve Conduction Testing

- Sensory nerve conduction testing will be conducted to detect neuropathy in all participants in Parts 2A, 3, and 4 of the study.
- A clinically significant abnormal nerve conduction value should be repeated within 24 - 48 hours from the initial test
- The nerve conduction procedure will be described in the Clinical Procedure Manual.
- Additional nerve conduction testing may be performed, if determined as necessary by the investigator.
- Refer to Section 7.1.4 for neuropathy specific stopping criteria.

8.2.5. Toronto Clinical Neuropathy Score for Polyneuropathy

- Tests and exams comprising Toronto Clinical Neuropathy Score System will be conducted to detect neuropathy in all participants in Parts 2A, 3, and 4 of the study Appendix 9).
- The details will be described in the Clinical Procedure Manual.
- Refer to Section 7.1.4 for specific stopping criteria.

8.2.6. Cognitive Assessment

- The MMSE will be conducted to detect changes in cognition in all participants in Parts 3 and 4 of the study (Appendix 9)
- The details will be described in the Clinical Procedure Manual.
- Refer to Section 7.1.4 for specific stopping criteria related to neurocognitive changes

8.2.7. Clinical Safety Laboratory Assessments

- See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study including during the follow up period should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant/any 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.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- 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.

8.2.8. Pregnancy Testing

- A blood pregnancy test must be performed for all female participants of childbearing potential before the administration of the first dose of study intervention as detailed in the SoA. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Refer to Section 1.3 for pregnancy testing during study intervention and post-treatment follow-up.
- If a pregnancy is reported then the Investigator should inform GSK within 24 hours of learning of pregnancy and should follow the procedures outlined in Section 8.3.5
- 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 study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AE or SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

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

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA (Section 1.3). However, SAEs that occur prior to the first administration of investigational medicinal product should be recorded only if assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests).
- All AEs will be collected from the start of intervention until the final follow-up visit at the time points specified in the SoA (Section 1.3).
- 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 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. 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 AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- For SAEs the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.4.
- 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Investigators have to report to the sponsor pregnancies, medication errors, abuse and misuse even in the absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the sponsor.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until completion of the final follow up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, 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.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- 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 10.3 (Appendix 3). 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 discontinue study intervention or be withdrawn from the study.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3 (Appendix 3). and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3.7. Adverse Events of Special Interest (AESIs)

8.3.7.1. AESIs specific to GSK3965193

8.3.7.1.1. Neuropathy and Neurocognitive events

Peripheral neuropathy events and neurocognitive events are categorized as Adverse Events of Special interest (AESIs) which must be reported to the Medical Monitor within 24 hours regardless of study drug relationship. Participants experiencing neurocognitive symptoms should be advised to avoid driving, operating heavy machinery or any other task that requires concentration and attention.

CCI [redacted]

Some neurocognitive events have been observed in the ongoing clinical study. The clinical monitoring strategy and stopping criteria are defined in Section 7.1.4

8.3.7.2. AESIs specific to Bepirovirsen

8.3.7.2.1. ALT Increases

The liver is a site of accumulation of antisense oligonucleotides and this has been exploited in the treatment of liver related diseases.

Outside the setting of disease reactivation or rebound viremia, the aetiology of ALT increase (flares) in CHB patients is currently uncertain. It has been postulated that ALT flares are evidence of reactivation of the immune system in the liver with accompanying clearance of infected hepatocytes, particularly when observed during immunotherapy or spontaneous loss of HBsAg. Therapeutic ALT flares have been shown to correlate with antiviral effect in blood (i.e. declines in HBV DNA, and/or HBsAg).

A monitoring strategy of ALT is presented in Section 10.6.

8.3.7.2.2. Vascular Inflammation and Complement Activation and Other Immune-mediated events

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

A monitoring strategy of vasculitis and complement activation is presented in Section 7.1.6.

8.3.7.2.3. 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 characterised 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 7.1.5.

8.3.7.2.4. Renal Injury

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

A monitoring strategy of renal function (e.g., SCr, uACR) is presented in Section 7.1.7.

8.3.7.2.5. Injection Site Reactions

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

8.3.8. Contact information for reporting SAEs, AESIs, pregnancies and stopping criteria

Contact information for reporting SAEs, AESIs, pregnancies and study stopping criteria

Study contact for questions regarding SAEs, AESIs and pregnancies Contact GSK's local and/or medical contacts Medical Contact: PPD PPD	**Study contact for reporting of study stopping criteria** If a stopping rule is met, the investigator must immediately inform the GSKs Local and/or Medical contacts. Medical Contact: PPD PPD
Contacts for reporting SAEs, AESIs and pregnancies Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com	**Backup study contact for escalation of stopping rules** Medical Contact: PPD PPD

8.4. Pharmacokinetics

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples collected for analyses of GSK3965193 plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study. Residual PK Plasma may also be analysed for other compound-related metabolites and the results reported separately.

Drug concentration information that may unblind the study will only be shared with the Drug Metabolism and Pharmacokinetics Study Director and scientists who are conducting and reporting the GSK3965193 metabolism study which is separate from this protocol. This information is needed to differentiate active-dosed participants from placebo to inform on the metabolite identification study conduct. It will not be reported to investigative sites or blinded personnel until the study has been unblinded.

In Part 4, samples will be collected for the PK analysis of GSK3965193 and bepirovirsen.

8.4.1. PK Plasma Sample Collection

Blood samples will be collected at all timepoints in Parts 1and 2 for measurement of plasma concentrations of GSK3965193 as specified in the SoA (Section 1.3). Blood samples will be collected at all timepoints in Parts 3 and 4 for measurement of plasma concentrations of GSK3965193 and bepirovirsen as specified in the SoA (Section 1.3).

GSK3965193 and bepirovirsen concentration analysis will be performed under the control of In Vitro/In Vivo Translation. Plasma concentrations of GSK3965193 and bepirovirsen will be determined using approved bioanalytical methodology.

The bioanalytical site will be detailed in the Laboratory Manual and raw data will be archived in the GSK R&D Good Laboratory Practice (GLP) archives.

A CCI [redacted] may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

8.4.2. Sample Collection for Metabolite Profiling

8.4.2.1. Plasma

Additional plasma was collected in Part 1 and Part 2A (Days 1 and 14) for analysis of circulating metabolites of GSK3965193 as specified in the SoA (Section 1.3). The results will be reported separately.

Residual PK samples collected for analyses of GSK3965193 plasma concentration may also be used to evaluate GSK3965193-relate metabolites.

8.4.2.2. Urine

Urine samples for analysis of GSK3915393 and its metabolites was collected in Parts 1 and 2A (Days 1 and 14) at the time-points listed in the SoA (Section 1.3) and the results reported separately. Details of urine sample processing, storage and shipping procedures are provided in the Laboratory Manual.

8.4.2.3. Bile

Duodenal bile samples were collected at the time-points listed in the SoA for the analysis of GSK3965193 and its metabolites for participants in the highest dose cohort in Part 2A only. Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatin capsule. The line unwinds after capsule swallowing as the capsule dissolves in the stomach and the line then passes into the duodenum. During withdrawal, the weighted section of the capsule separates from the line and passes in the stool. Additional details of the bile EnteroTracker sample collection, processing, storage and shipping procedures were provided in the Laboratory Manual. These samples may then be analysed for compound-related material and the results reported separately.

8.5. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. If the sample is not collected on Day 1 as per the SoA, it may still be collected at any time in the study if the participant changes their mind or if the sample collection were missed.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 [Genetics] for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.6. Biomarkers

Blood samples CCI [redacted] will be used to evaluate virologic, target engagement, disease and immune biomarkers and assays related to the pathogenesis of chronic HBV infection and the participant's response to GSK3915393 and/or bepirovirsen (Part 3 optional and Part 4).

Serum sample biomarkers include 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.

If allowed by country regulation/ethics, biomarker sampling may be conducted remotely by a HHS professional.

GSK may store samples for CCI [redacted] after the end of the study to achieve study objectives. The archived 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.). Additionally, with participants' consent, samples may be used for further research by the GSK or others such as universities or other companies to contribute to the understanding of chronic hepatitis B or other diseases, the development of related or new treatments or research methods.

8.7. HBV Resistance Monitoring

HBV DNA/RNA sequencing samples may be used for HBV resistance mutation analysis.

CCI [redacted]

Sequencing of the virus will be attempted at baseline to identify pre-existing HBV genetic polymorphisms and to determine the viral genotype (e.g., genotype A, B, C, D). Patients on stable NA therapy often have insufficient levels of viral DNA and RNA to sequence, therefore previously determined viral genotype information will be collected when available. Serology may also be used to determine the viral genotype.

CCI [redacted]

8.7.1. Resistance Analysis based upon HBV DNA Criteria (Parts 3 and 4)

HBV DNA for each participant will be measured throughout the study. CCI [redacted]

CCI [redacted]

8.7.2. Resistance Analysis based upon HBsAg Criteria (Parts 3 and 4 only)

This applies to Part 3 optional bepirovirsen treatment and in Part 4. HBsAg levels for each participant will be measured throughout the study. In addition to monitoring defined above, CCI [redacted]

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GSK.

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

Complete details of the planned statistical analyses will be provided in the statistical analysis plan (SAP). Any deviations from the planned analyses will be described in a SAP addendum and justified in the final integrated clinical study report.

9.1. Statistical Hypotheses

No formal hypotheses will be tested.

The primary objectives of Parts 1 and 2 of this study were to assess the safety and tolerability of single and repeat ascending doses of GSK3965193 in healthy participants. Descriptive statistics were used to assess safety and tolerability objectives. Treatment comparisons with placebo were based on review of descriptive statistics and individual participant data. The pharmacokinetics of GSK3965193 after administration of single and repeat doses of GSK3965193 in healthy participants were also determined. CCI [redacted]

The primary objectives of Part 3 and 4 are to assess the safety, tolerability, PD and efficacy CCI [redacted] of GSK3965193 monotherapy (Part 3) or in combination with bepirovirsen (Part 4) in PLWCHB on stable NA therapy.

For Part 3, CCI [redacted]

For Part 4, CCI [redacted]

9.2. Sample Size Determination

The planned number of evaluable participants will be CCI and allocated as follows:

Part 1: CCI

Part 2A: CCI

Part 2B: CCI

Part 3: CCI

Part 4: CCI

CCI

Table 10 CCI

CCI

CCI [redacted]

[redacted].

Table 11 CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

Part 3

CCI [redacted]

CCI [redacted].

Table 12 CCI [redacted]

CCI [redacted]

Part 4

CCI [redacted]

Table 13 CCI

CCI

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who passed screening and entered the study.
Intent-to-Treat (ITT)	All participants who received at least 1 dose of study treatment. This population will be based on the treatment the participant was randomized to.
Safety	All participants who received at least 1 dose of study treatment. This population will be based on the treatment the participant received.
Pharmacokinetic (PK) Concentration	All participants in the Safety population who received an active study treatment and had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be used for PK concentration listing.
Pharmacokinetic Parameter	All participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.
Pharmacodynamic (PD)	All participants in the Safety population for whom a Pharmacodynamic sample was obtained and analysed.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to First Participant First Visit (FPFV) for each study part and it 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. Exploratory analyses will be described in the SAP.

CCI [redacted]

9.4.1. General Considerations

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.

9.4.2. Primary Endpoint(s)

A primary objective for Parts 1-4 is to assess the safety and tolerability of oral administration of GSK3965193. The primary safety endpoints include incidence of AEs, SAEs, withdrawals due to AEs, incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, and cardiac parameters (ECG), and sensory nerve conduction (Parts 2A, 3, 4). The description of the safety analysis is in Section 9.4.5.

Parts 1 and 2:

A primary objective for Parts 1 and 2 was to evaluate the PK characteristics of single and repeat doses of GSK3965193. The description of pharmacokinetic analysis is in Section 9.4.7.

Part 3:

A primary objective for Part 3 is to evaluate PD effect of GSK3965193 monotherapy in PLWCHB. The PD analyses will be based on the ITT population.

The first main estimand supporting this primary objective for Part 3 is defined as:

- **Population:** PLWCHB treated on stable NA therapy
- Treatments: Dose of GSK3965193, Placebo

- Variable:
  - Continuous: Maximum reduction of serum HBsAg levels from baseline CCI [redacted]
- Intercurrent Events: CCI [redacted]
- Population-level Summary:
  - Continuous: CCI [redacted]

For the maximum reduction of serum HBsAg levels from baseline CCI [redacted]

Part 4:

A primary objective for Part 4 is to evaluate efficacy of GSK3965193 in combination with bepirovirsen in PLWCHB. The efficacy analyses will be based on the ITT population.

The second main estimand supporting this primary objective for Part 4 is defined as:

- Population: PLWCHB treated on stable NA therapy
- Treatments: Bepirovirsen, Placebo for Arm 1; GSK3965193, bepirovirsen for Arm 2
- Variables:
  - Achieve SVR (undetectable serum HBV DNA and HBsAg for 6 months after the planned end of treatment of bepirovirsen)
- Intercurrent Events:
  - Intercurrent event of discontinuation of, interruption in, and non-adherence to GSK3965193 not related to any wide disruptive events and for change in the background NA therapy will be CCI [redacted]
  - Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to bepirovirsen and GSK3965193 will be handled assuming CCI [redacted]
- Population-level Summary: Proportion of PLWCHB

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

Details of the statistical analyses will be provided in the SAP.

9.4.3. Secondary Endpoint(s)

The first secondary objective is to evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB of Part 3. The description of pharmacokinetic analysis is in Section 9.4.7.

Part 3:

A secondary objective for Part 3 is to evaluate the PD effect of GSK3965193 monotherapy in PLWCHB. The PD analyses will be based on the ITT population.

The third main estimand supporting this secondary objective for Part 3 the same as the first main estimand supporting the primary PD objective for Part 3, except the following:

- Variable:
  - Categorical: ≥0.5x log10 IU/mL reduction of serum HBsAg levels from baseline loss of HBsAg any time during the study
- Population-level Summary:
  - Categorical: Proportion of PLWCHB

CCI [redacted]

Part 4:

A secondary objective for Part 4 is to evaluate the PD effect of GSK3965193 in combination with bepirovirsen in PLWCHB.

The fourth main estimand supporting this secondary objective for Part 4 is defined the same as the second main estimand supporting the primary efficacy objective for Part 4, except that the variable is PLWCHB experiencing HBsAg loss anytime during the study.

CCI [redacted]

9.4.4. Tertiary/Exploratory Endpoint(s)

Exploratory analyses will be described in the SAP, however for optional sequential treatment with bepirovirsen, summary tables will only be generated if at least 5 participants choose to take part in the open label extension.

9.4.5. Safety Analysis

All safety analyses will be performed on the Safety Population.

Descriptive statistics will be used to assess safety and tolerability objectives. No formal statistical analyses of safety data are planned. Data will be summarized according to GSK Integrated Data Standards Library standards. In addition, individual participant data will be reviewed. Treatment comparisons with placebo will be based on review of descriptive statistics and individual participant data.

9.4.6. Other Analysis

Descriptive statistics will be used to assess biomarker profile changes and to explore metabolism of GSK3965193. Details of the analyses will be provided in the SAP.

9.4.7. Pharmacokinetic Analyses

To evaluate the PK characteristics of single and repeat doses of GSK3965193 was the primary objective of Parts 1 and 2. To investigate CCI [redacted] on the PK characteristics of CCI [redacted] of GSK3965193 was the secondary objective of Part 2B. To evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB is the secondary objective of Part 3.

- Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK or delegate.
- Plasma GSK3965193 concentration-time data (intense sampling in Parts 1, 2, and 3) will be analyzed CCI [redacted]
- From the plasma concentration-time data, the following PK parameters, in addition to others, will be determined, as data permit per part:
  - maximum observed blood concentration (Cmax)
  - time to Cmax (Tmax)
  - area under the plasma concentration-time curve [AUC(0-t), AUC(0-inf), and AUC(0-τ)]
  - apparent terminal phase half-life ($T_{1/2}$)

- Dose proportionality were assessed following single doses of GSK3965193 (Part 1) for AUC(0-inf) and Cmax and following repeated dosing in Part 2A for AUC(0-τ) and Cmax on Days 1 and 14 using the power model, and following repeated dosing in Part 3 for AUC(0-τ) and Cmax on Days 1 and 28 using the power model.
- Accumulation will be evaluated for each dose by determining the ratio of Day 14 (Parts 2A and 3) to Day 1 AUC(0-τ) (R(AUC(0-τ)), Cmax (R(Cmax)), and Cτ(R(Cτ)). C24 on Day 1 will be taken as the Cτ on that day.
- Steady-state of GSK3965193 concentrations will be assessed in Parts 2A and 3 by estimating the slope of pre-dose trough concentration levels CCI [redacted] by dose.
- The CCI [redacted] on the PK of GSK3965193 (AUC(0-inf), and Cmax) will be examined by fitting an analysis of variance model separately to each of the log-transformed PK parameters with period and treatment CCI [redacted] as fixed effects and participant as a random effect.

Details on the statistical analyses will be described in the SAP.

9.4.8. Pharmacokinetic/Pharmacodynamic Analyses

PK-PD analysis may be conducted in a separate report, as data permits. A modelling approach will be considered to describe the relationship between GSK3965193 concentration and QTc data.

9.5. Interim Analysis

Parts 1 and 2

All preliminary safety, tolerability and available pharmacokinetic data were reviewed by the DEC prior to each dose escalation or administration according to the dose escalation charter. The details of the Bayesian analysis for dose escalation were described in the SAP.

Unblinded data from Parts 1, 2A and 2B were reported out in full following the last participant last visit in each of these parts of the study and prior to the conclusion of the study.

Part 3

In Part 3, CCI [redacted]

Additional interims may be considered to support clinical development and terminate the study early if appropriate.

Details of all interim analyses will be described in the SAP.

Part 4

Interim analyses CCI [redacted]

Details of the futility analysis will be described in the SAP.

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:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, 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 IEC/IRB 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:
  - 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/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her LAR and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 45 days from the previous ICF signature date.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3965193 and/or bepirovirsen or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3965193 and/or bepirovirsen approved for medical use or approved for payment coverage.

Sample testing will be done in accordance with the recorded consent of the individual participant/LAR(s).

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 ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. 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. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other 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 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.

10.1.5. Committees Structure

10.1.5.1. Safety Data Review

- An 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 contributes to the continual assessment of incoming new efficacy and safety information.

- For Parts 1 and 2, participant safety will be monitored by members of the DEC, which is comprised of members of the study team and the Principal Investigator (or designate).
- For Part 3 and 4, participant safety will be continuously monitored by an internal SRT, which includes safety signal detection at any time during the study. Blinded data will be reviewed. The SRT will include a subset of the study team whose responsibility is to provide a forum for the proactive, aggregate, and holistic evaluation of the safety profile for the product over its lifecycle.
- In Parts 3 and 4 an IDMC will be involved in review of safety data as follows:
    - Part 3 – open-label bepirovirsen safety data will be reported to the IDMC once all participants who receive bepirovirsen have completed treatment. Unblinded safety data for GSK3965193 in Part 3 will also be shared with the IDMC for awareness prior to the start of Part 4.
    - Part 4 – the IDMC will provide full unblinded safety oversight.
- The IDMC will operate according to an IDMC charter.
- All safety data collected will be summarized and reviewed by the IDMC for agreement of next steps.

In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause/stop the study.

- Any deaths, regardless of causality
- Any drug-related SAEs
- Two or more participants in the same dose group/cohort experience non-serious severe AEs (≥Grade 3) considered at least possibly drug-related
- Additional criteria specified in Section 7.1

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date (adult populations). 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.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Quality tolerance limits will be pre-defined in the trial master file to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF 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 the source data acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

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 of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or 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 suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- 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

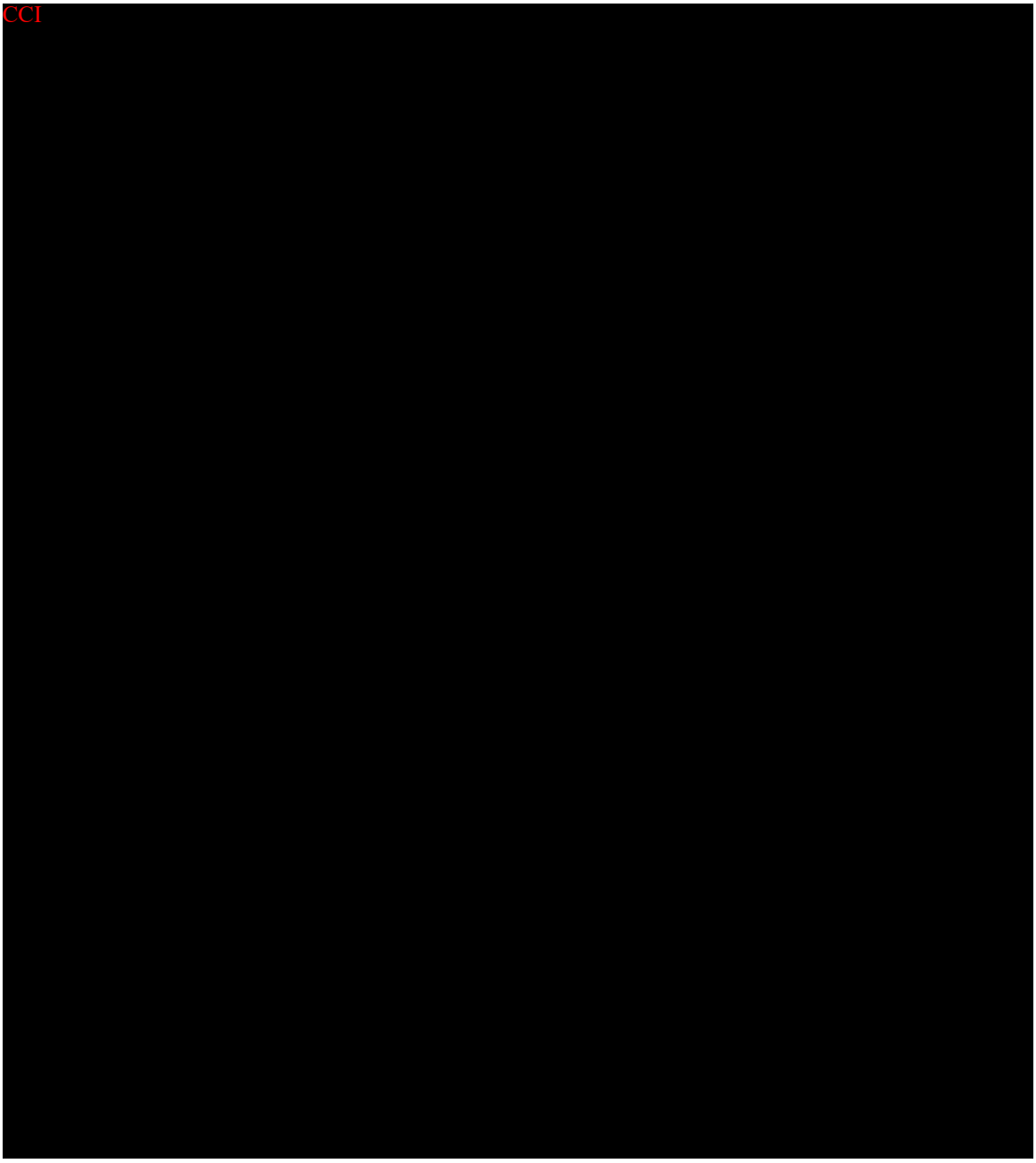
The tests detailed in Table 14 will be performed by the local or central laboratories as documented in the Laboratory Manual.

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.

Table 14 Protocol-Required Tests

CCI



CCI

[redacted]

CCI

[redacted]

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 <u>Meeting</u> 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 conditions 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). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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). • 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. • 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any serious adverse event that, at any dose:
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

An SAE is defined as any serious adverse event that, at any dose:
"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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations: • Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (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 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure

Cardiovascular Events (CV) Definition:
• Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

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, 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 GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • 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.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment of severity should be made using the appropriate grading table and parameter in The DAIDS Table [DAIDS, 2017]. Each DAIDS parameter has criteria defined for severity Grades 1 to 4, all deaths related to an AE are to be classified as Grade 5. The DAIDS Table is available at the following link: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf • An event is defined as severe if it is Grade 3 or above. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. 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** GSK**.**
- Where multiple interventions are administered in the same visit, the investigator should specify, when possible, if the AE/SAE could be causally related to a specific study intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the AE/SAE to be related to all interventions.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.

Follow-up of AE and SAE
• The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information. • After the initial AE/SAE the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK 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 off-line 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 off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator 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 the Section 8.3.8.

SAE Reporting to GSK via Paper Data Collection Tool
• Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of email 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 time frames. • Contacts for SAE reporting can be found in Section 8.3.8.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are considered WONCBP

- **Premenarchal**
- **Premenopausal female with 1 of the following:**
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Notes: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
- **Postmenopausal female**
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methodsb That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulationc • oral • injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

10.4.3. Collection of Pregnancy Information

Information regarding all pregnancies in female participants and female partners of male participants will be collected as follows:

- Investigators will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (pregnant participant).
- Investigators will collect pregnancy information on any female partner of a male participant, who becomes pregnant whilst the male participant is participating in this study (pregnant partner).
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's or participant's partner's pregnancy.
- The pregnant participant/partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant/partner and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Section 10.3 (Appendix 3). 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:

- will discontinue study intervention or be withdrawn from the study

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3965193 and/or bepirovirsen or CHB and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3965193 or other PAPD5/7 inhibitors, bepirovirsen or other ASOs, and CHB. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3965193 and/or bepirovirsen or study interventions of these classes. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3965193 and/or bepirovirsen (or study interventions of these classes) or CHB continues but no longer than 20 years after the last subject last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Parts 1, 2, and 3 (GSK3965193 monotherapy) Liver chemistry stopping criteria and required follow up assessments

Liver chemistry stopping criteria and required follow up assessments

CCI

[redacted]

Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended	• Viral hepatitis serology[4] • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis, within 48 hours of last dose[5] • Serum GGT, CPK, LDH 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 CRF • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter

Liver Chemistry Stopping Criteria	
For all other stopping criteria (bilirubin ≤2xULN and INR <1.5): • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24-72 hrs • Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits. **RESTART or RECHALLENGE** • Do not restart or rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol-specified follow-up assessments.	medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5 obtain the following in addition to the assessments listed above:** • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury. • 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 specialist if available: – In patients when serology raises the possibility of AIH. – 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 conducted, then complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen, Hepatitis B virus DNA load and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Hepatitis D antibody, Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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.

Part 3 (Bepirovirsen Monotherapy) and Part 4

Phase 2 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

The procedures listed below are to be followed if a participant meets any of the liver chemistry stopping criteria defined in Section 7.1.1.

- Immediately withdraw the participant from study treatment.
- Notify the Medical Monitor within 24 hours of learning of the abnormality to confirm the participant's study treatment cessation and follow-up.
- Complete the Liver Event CRF.
- Complete the "Safety Follow-up Procedures" listed below

Safety Follow-up Procedures for Participants Who Meet Any of The Stopping Criteria:

Viral hepatitis serology including:

1. Hepatitis A IgM antibody;
2. Cytomegalovirus IgM antibody;
3. Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
4. Hepatitis E IgM antibody;
5. Hepatitis C virus RNA load;
6. Hepatitis D virus antibody;
7. Hepatitis B virus DNA;

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

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

The following are required for participants who meet the ALT and bilirubin stopping criteria but are optional for other abnormal liver chemistries.

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

10.7. Appendix 7: Covid-19

10.7.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

10.7.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.7.3. Protocol Defined Procedures/Visits

The protocol defined interval for the collection of samples during the Follow-up visit (see Section 1.3 Schedule of Activities) may be extended up to a maximum length of 14 days.

10.7.4. Data Management/Monitoring

If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

eCRF/CRF Final or Interim Sign off Process: The PI is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.8. Appendix 8: Toronto Clinical Neuropathy Scoring System

Toronto Clinical Neuropathy Scoring System (TCNS) has been developed for detecting and staging polyneuropathy, based on symptoms and/or signs [Bril, 2002]. This scale is valid and reliable for the diagnosis and staging of diabetic and non-diabetic polyneuropathy [Perkins, 2002; Bril, 2002; Abraham, 2018]. The TCNS incorporates sensory and motor symptoms, and lower-limb sensory and reflex findings as illustrated in the table below.

Symptom Scores	Reflex Scores	Sensory Test Scores *
Foot	Knee reflexes	Pinprick
Pain	Ankle reflexes	Temperature
Numbness		Light touch
Tingling		Vibration
Weakness		Position
Ataxia		
Upper limb symptoms		

* Sensory testing should be conducted on the first toe

The score ranges from a minimum of 0 (no neuropathy) to a maximum of 19 points, and is graded as:

- symptom score: present = 1, absent = 0
- reflex score: absent = 2, reduced = 1, normal = 0
- sensory test score: abnormal = 1, normal = 0

Polyneuropathy severity is graded as:

- 0–5, no or minimal neuropathy
- 6–8, mild neuropathy
- 9–11, moderate neuropathy
- ≥12, severe neuropathy

10.9. Appendix 9: Mini-Mental State Examination (MMSE)

The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The MMSE has demonstrated validity and reliability in psychiatric, neurologic, geriatric, and other medical populations [Folstein, 1975].

10.10. Appendix 10: Study-Specific Information

The Study Reference Manual (SRM) is no longer in use and the following sections were transferred from the SRM.

10.10.1. Time Deviation Windows for Outpatient Visits

Where possible, study visits should be performed on the planned study day according to the protocol Schedule of Activities (SoA) Section 1.3.

10.10.2. Timing of Assessments, Window Allowances and Order of Procedures

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws, so that the timing of the assessments allow the PK and biomarker blood draw to occur during the permitted time windows. Timing of vital signs, 12-lead ECGs and safety blood draws may be adjusted accordingly.

For pre-dose assessments on Day 1, it is recommended to follow the aforementioned order; however, it will not be considered as a protocol deviation if another order is required for logistical purposes.

As per SoA in the study protocol, PK samples should be collected immediately after the time of ECG extraction in order to avoid autonomic changes in heart rate associated with blood sampling. It is important to note that immediately is considered as 2-3 minutes.

Please ensure that timing of assessments and order of procedures is consistent throughout the study for each participant.

All study staff should time study procedures/assessments using the same clock, typically this will be the wall clock in the participant room/cubicle.

Personal watches, iPads or mobile telephones should not be used to time study assessments or procedures; neither should the time stamp from electronic charts be used, when this reflects the time of charting.

Consistent use of a single time source will also limit the number of potential data queries related to time windows.

Procedure	Time point	Acceptable window of assessment
Physical Assessment	CCI [redacted]	
ECG		
Vitals		
SNCV		
Nerve Function Exam for Toronto Clinical Neuropathy Score (TCNS)		

10.11. Appendix 11: Country-Specific Requirements

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the selection of study population and the withdrawal criteria

A participant will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).

It is the investigator's responsibility to ensure and to document (in the source document - participant notes) that the participant is affiliated to or beneficiary of a social security category.

Participants will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Participants not completing the study for whatever reason could be compensated generally on a pro rata basis.

2. Concerning the study governance considerations

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

  ⇒ Concerning **the process for informing the participant** and/or his/her legally authorized representative, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the participant and/or his/her legally authorized representative written consent. It also contains a reference to the single scientific and ethical regulatory authorisation.

  ⇒ **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

  French Patient Informed Consent Form is in duplicate.

  The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

  In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **INFORMATION TO THE HOSPITAL PHARMACIST**

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the data management the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the participants recruited in this clinical trial (subject number, treatment number, participants status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

*"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

10.12. Appendix 12: Abbreviations, Definition of terms and Trademarks

%CVb	between-participant coefficient of variation
%CVw	within-participant coefficient of variation
ACAT	advanced compartmental absorption and transit (model)
uACR	Urine albumin to creatinine ratio
AE	adverse event
AF	Atrial Fibrillation
AICD	Automatic implantable cardioverter defibrillator
ALT	alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic antibody
Ang II	AngiopoietinII
Anti-HBeAg	hepatitis B virus e-antigen antibody
Anti-HBsAg	hepatitis B virus surface antibody
APRI	aspartate aminotransferase-platelet index
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0-24)}$	area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose
$AUC_{(0-\infty)}$	area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BID	twice daily
bpm	beats per minute
CA	Competent Authority
CGRP	calcitonin gene-related peptide
CHB	chronic hepatitis B
CI	confidence interval
CKD-EPI	chronic kidney diseases epidemiology collaboration
cm	centimeter
Cmax	maximum observed concentration
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
CVb	between-participant coefficient of variation
CVw	within-participant coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DEC	Dose Escalation Committee
DILI	drug-induced liver injury
dL	deciliters

DNA	deoxyribonucleic acid
DoR	delegation of responsibilities
EC	Ethics Committee
EC_{90}	concentration that produces 90% of maximal effect
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FPFV	first participant first visit
FSH	follicle stimulating hormone
FTIH	first-time-in-human
g	gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
H	hours
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B virus e-antigen
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HRT	hormonal replacement therapy
hs-CRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IU	international units
Kg	kilograms
kPa	kilopascals
L	liters
LAR	legally authorized representative
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification

m^2	Meter square
MABEL	minimally anticipated biologic effect level
MAD	multiple ascending dose
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligrams
Min	minutes
mL	milliliters
MMSE	mini-mental state examination
MOE	methoxyethyl
MSDS	material safety data sheet
Msec	milliseconds
NA	nucleos(t)ide analog
NCV	Nerve conduction velocity
ng	nanograms
NOAEL	no observed adverse effect level
NQ	non-quantifiable
Nucleos(t)ide	nucleoside or nucleotide
OAT	organic anion transporter
OCT	organic cation transporter
PACAP	pituitary adenylate cyclase-activating polypeptide
PAPD5/7	non-canonical poly A RNA polymerases PAPD5 and PAPD7
PBMC	peripheral blood mononuclear cells
PBPK	physiologically based pharmacokinetics
PD	pharmacodynamics(s)
PHH	primary human hepatocytes
PI	principal investigator
PK	pharmacokinetic(s)
PLWCHB	participants living with chronic hepatitis B infection
PT	prothrombin time
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	Fridericia’s QT correction formula
RAP	Reporting and Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
RNase H	ribonuclease H
RTMS	Randomisation and Trial Supply Management System
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SDV/SDR	source data verification/source document review
siRNA	small interfering ribonucleic acid
SNCV	sensory nerve conduction velocity
SoA	schedule of activities

SRM	Study Reference Manual
SRT	Safety Review Team
t½	terminal half-life
TCNS	Toronto clinical neuropathy score
tmax	time of maximum observed concentration
µg	micrograms
ULN	upper limit of normal
µmol	micromole
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

Term	Definition
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthoried AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
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. 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.
Combination product	Combination product comprises any combination of: • drug • device • biological product. Each drug, device and biological product included in a combination product is a constituent part.
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.
HHS	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
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.
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.
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.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
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).
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.
Remote visit	A visit conducted in the place other than the study site.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to 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.
TM	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
NONE

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GastroPlus
EnteroTracker
MedDRA
WinNonlin

10.13. Appendix 13: Protocol Amendment History

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

Amendment 09: 22 July 2024

Overall rationale for the Amendment: Changes were provided in this amendment in response to questions by a regulatory agency.

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]	Adjusted timings of baseline urine assessments, removed duplicate urine drug test	Minimise test burden and ensure appropriate timing of baseline assessments
5.2.2 Exclusion Criteria for PLWCHB	Updated exclusion criterion 24 to specifically mention mental health conditions	Ensure that mental health conditions are explicitly mentioned to ensure due consideration in evaluation of exclusion criteria
5.2.2 Exclusion Criteria for PLWCHB	Specified the year of derivation for the CKD-EPI formula to be used for GFR calculations	Ensure the intended formula is used across sites
6.1 Study Intervention(s) Administered	Additional rows and information added regarding roles of products used within the trial	Clarify all details relating to roles of products used within the trial
6.8 Concomitant Therapy	CCI [redacted]	Align protocol provided information with Investigator's Brochure
8.3.7.1 Neuropathy and Neurocognitive events	Added information to indicate that participants experiencing neurocognitive symptoms should be advised to avoid driving and operating heavy machinery.	Align protocol provided information with Investigator's Brochure and Patient Information Sheet/ICF
10.2 Appendix 2: Clinical Laboratory Tests	Specified the CKD-EPI formula to be used for GFR calculations	Ensure the intended formula is used across sites
10.2 Appendix 2: Clinical Laboratory Tests	Clarified that urinalysis may be performed using automated systems	Ensure methods of urinalysis are accurately described

Amendment 08: 26 March 2024

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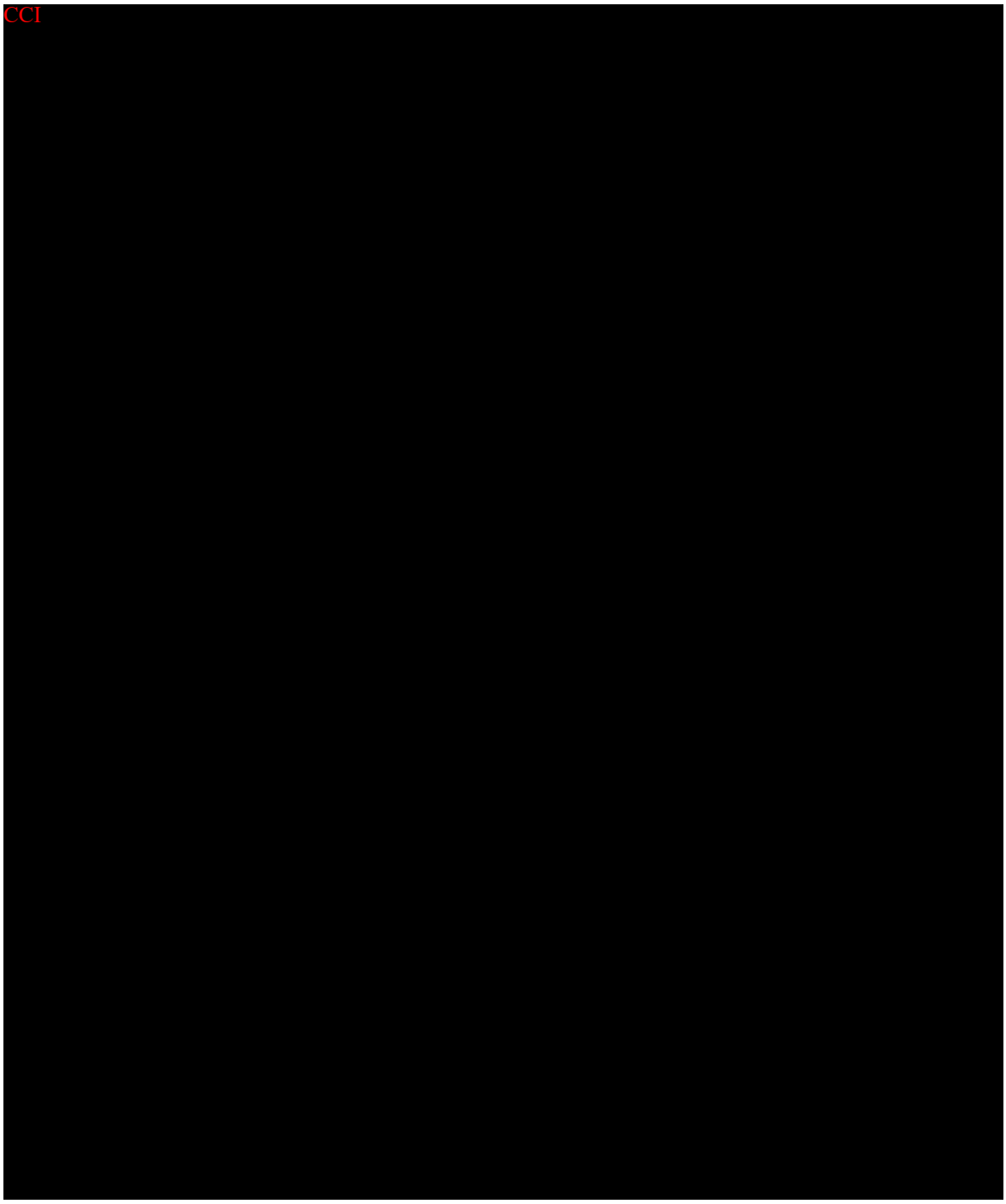
CCI



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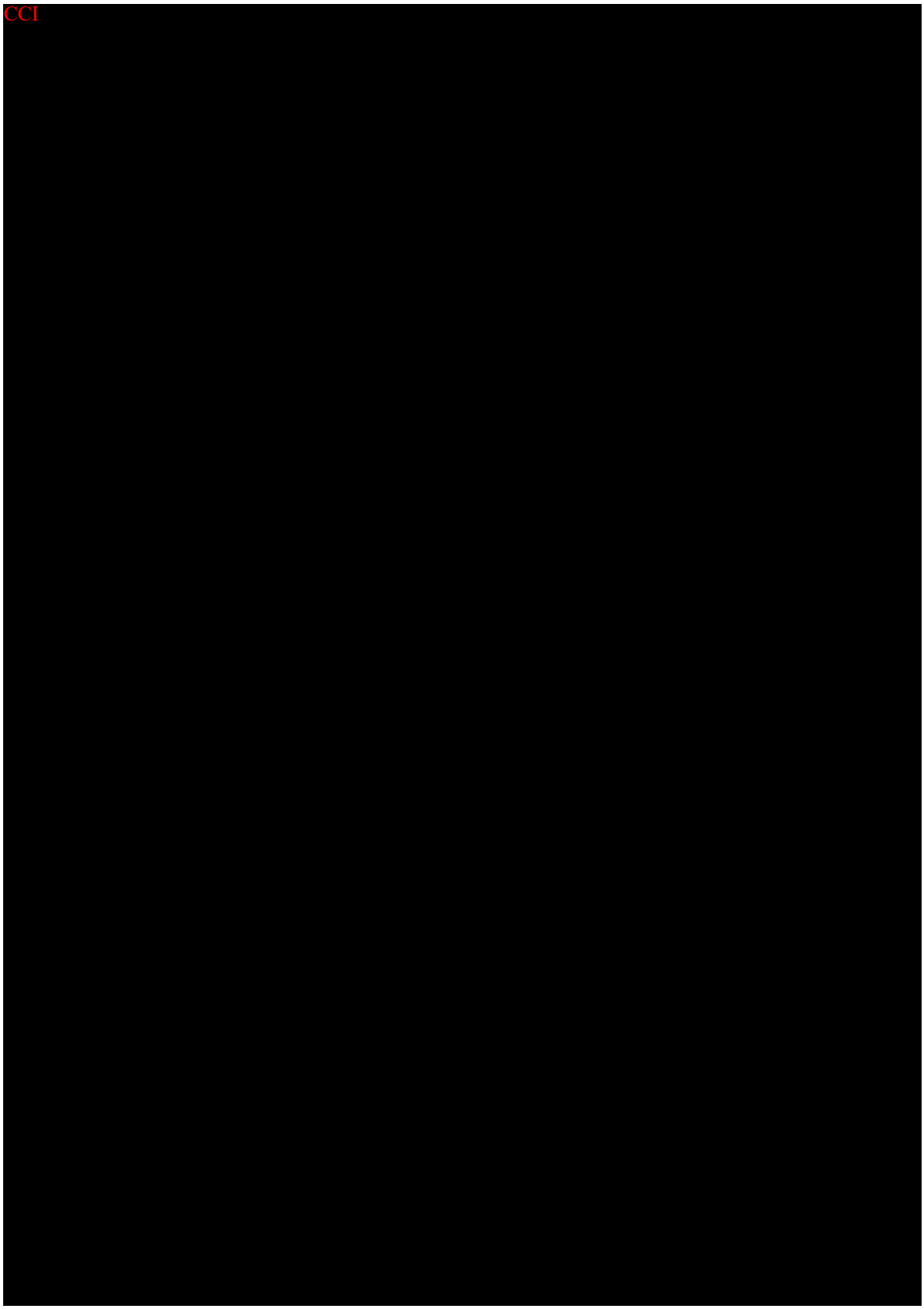

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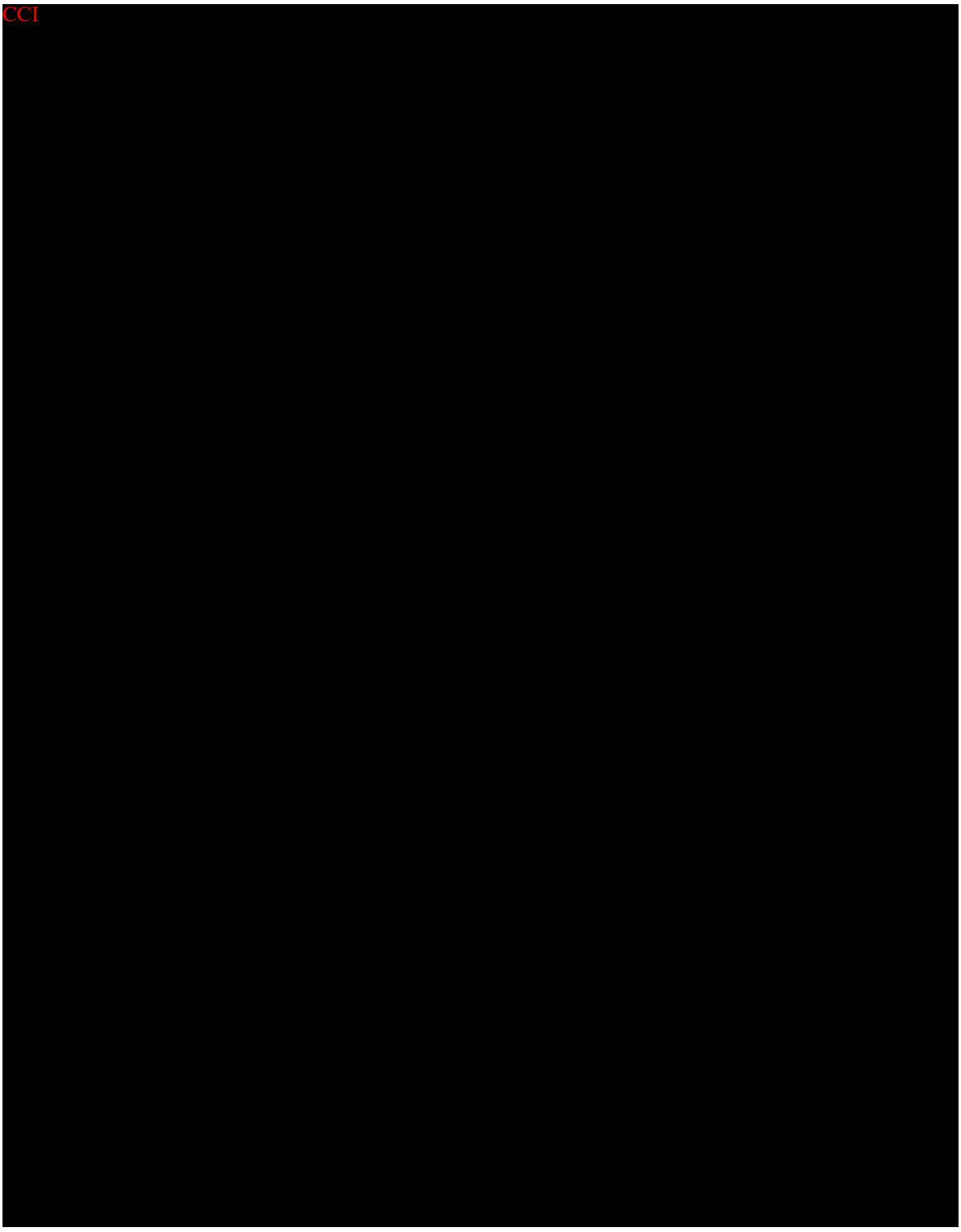

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Amendment 07, 29 January 2024

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Amendment 06, 01 December 2023

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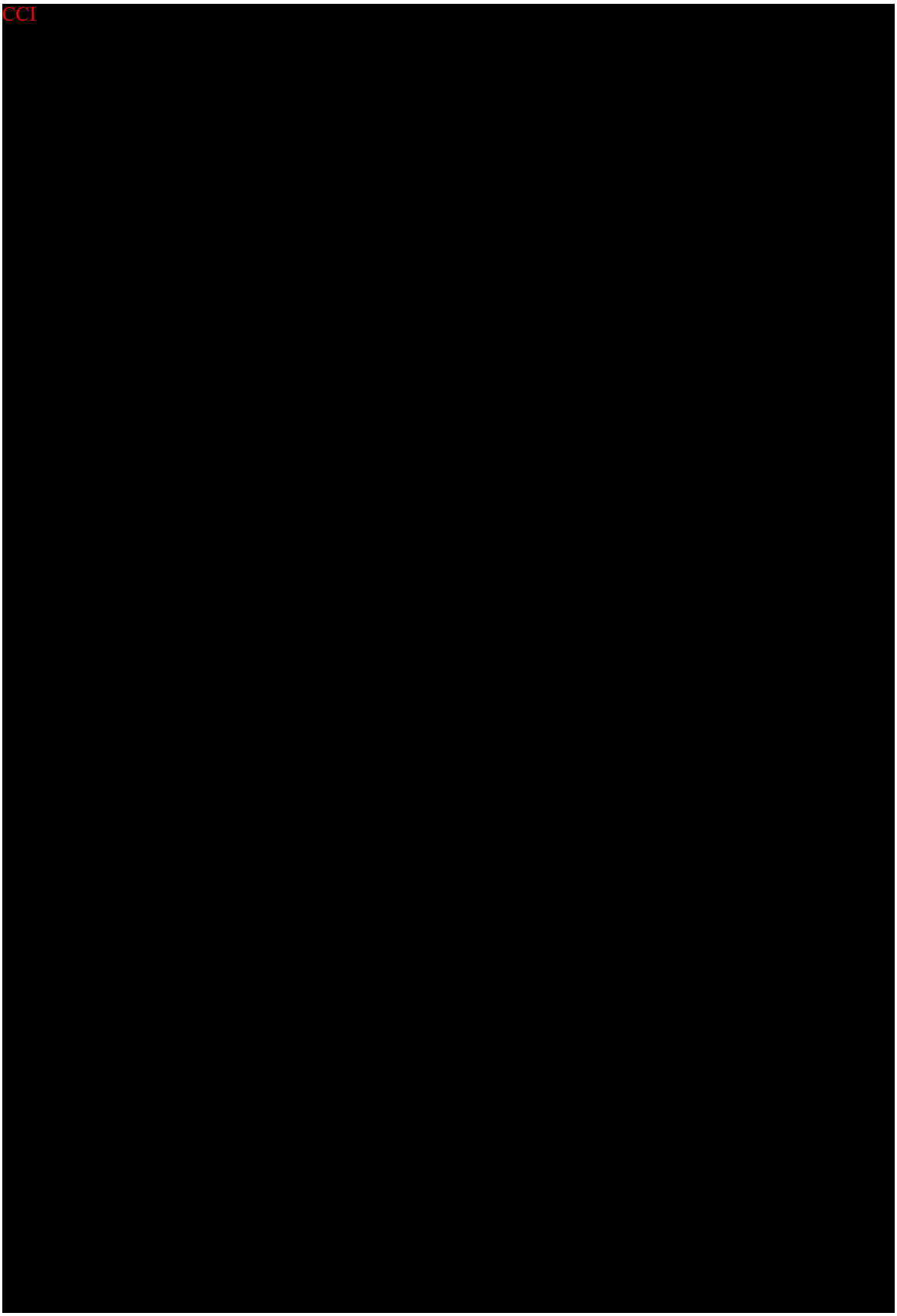

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Amendment 05, 09 March 2023

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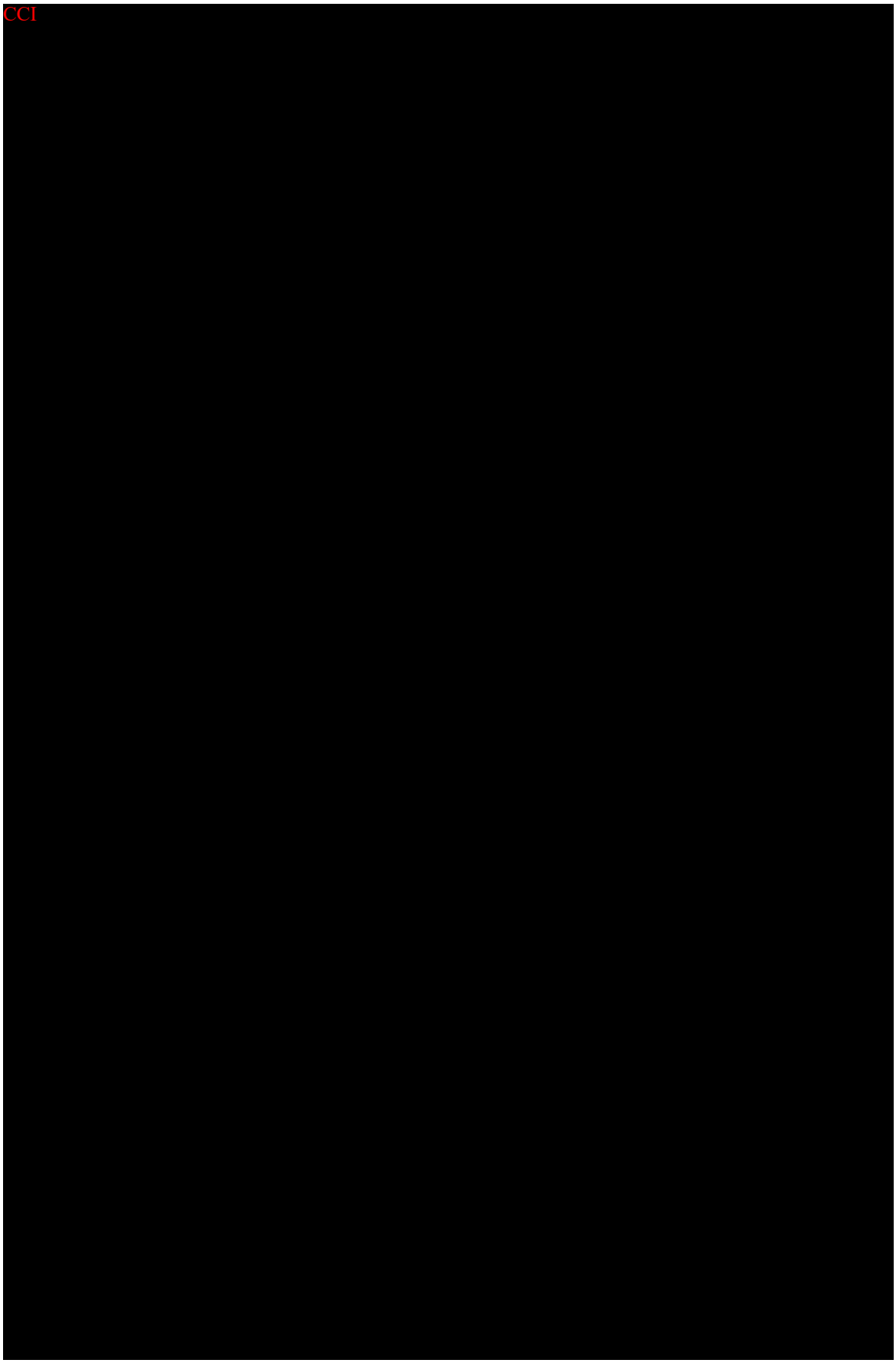

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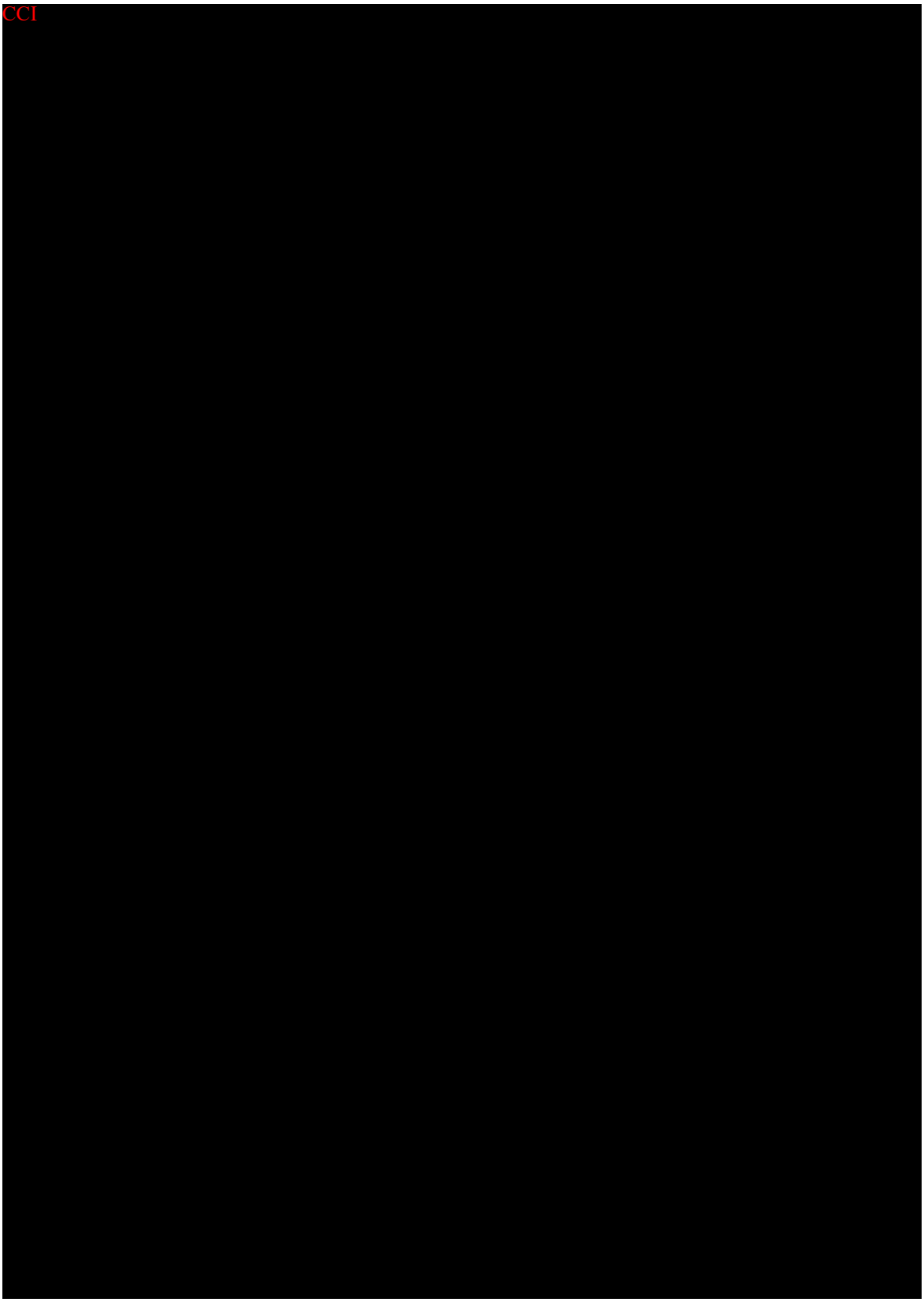

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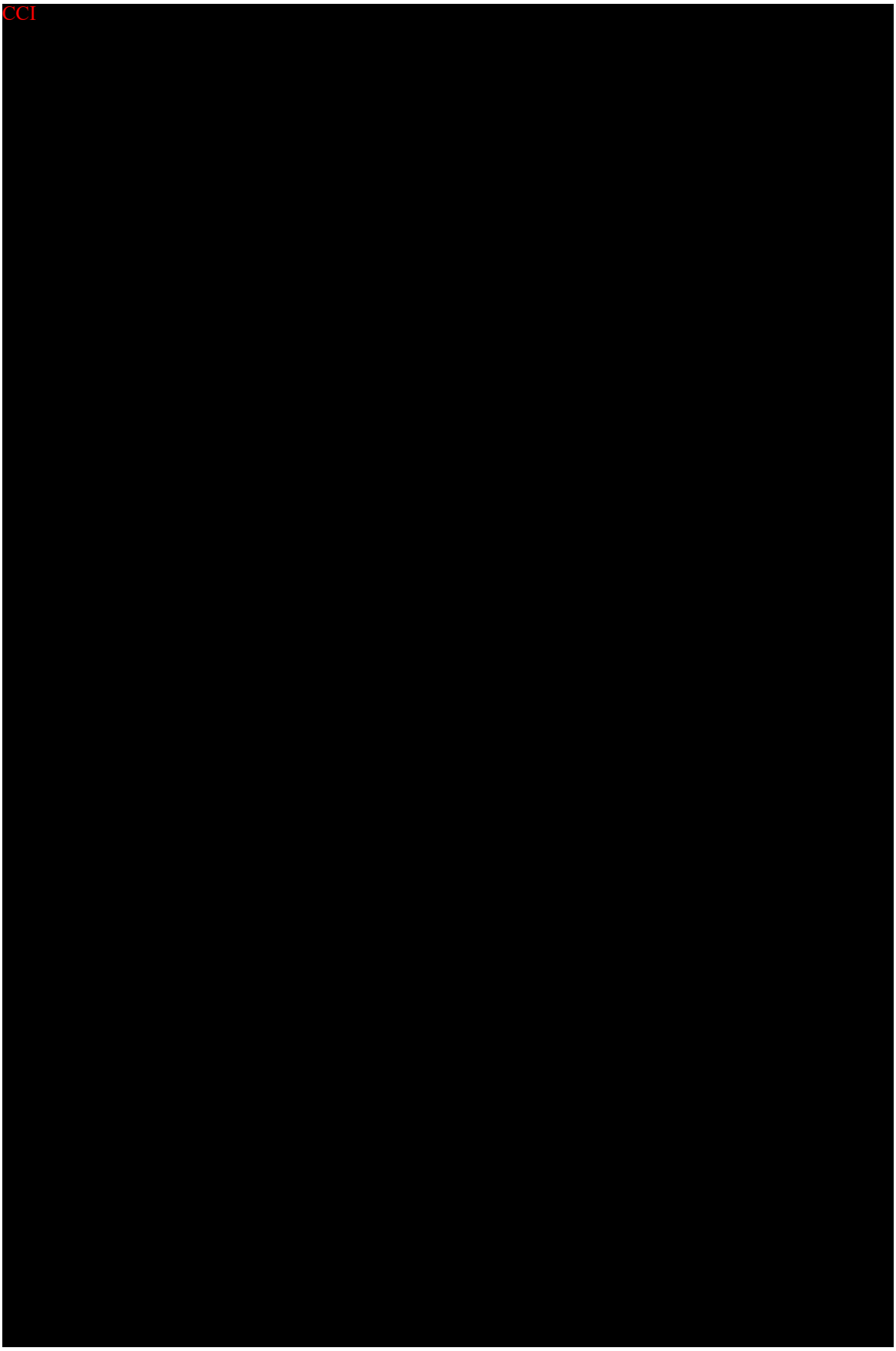

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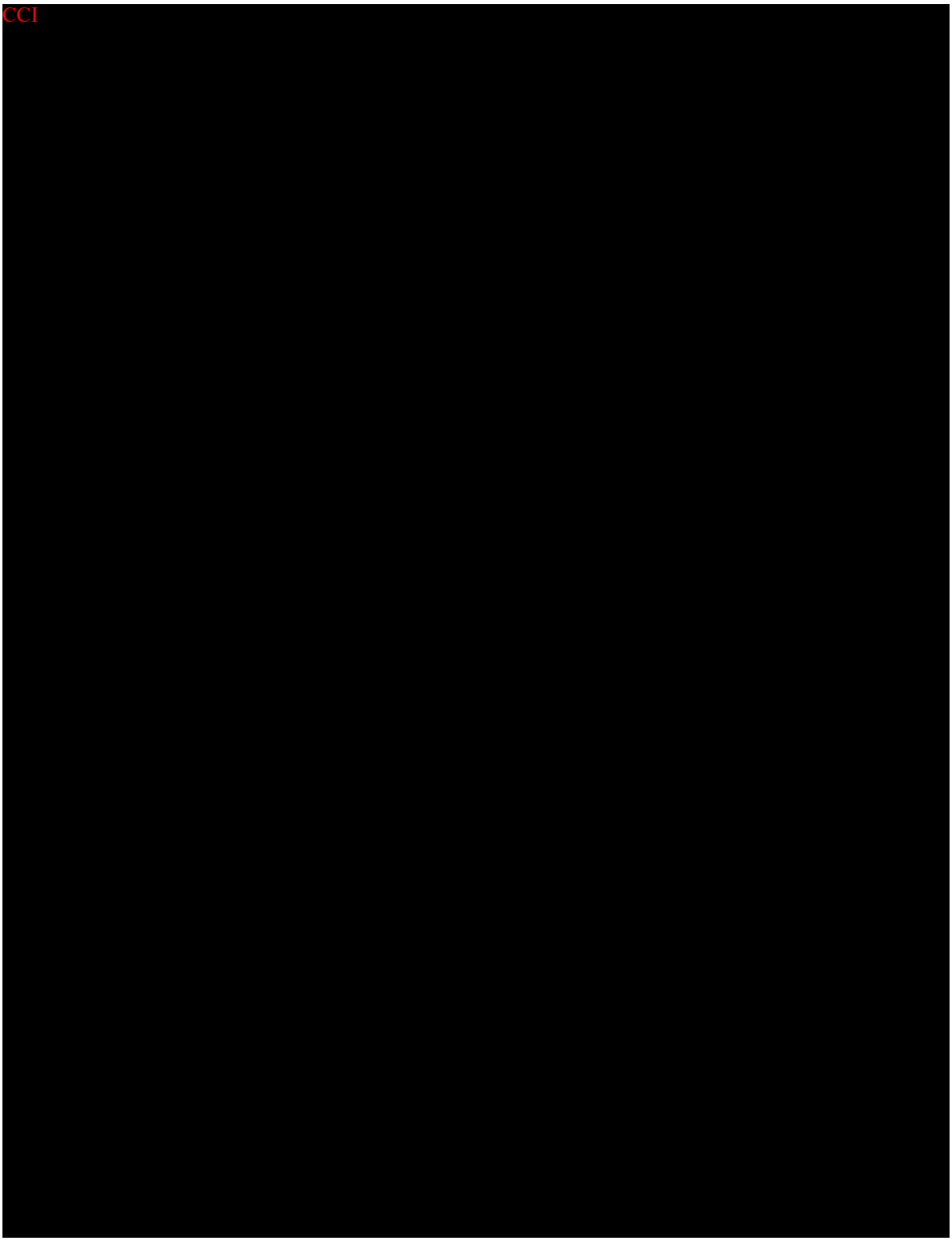

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Amendment 03, 26 August 2022

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Amendment 02: 25 April 2022

CCI

[redacted]

CCI

[redacted]

Amendment 01: 31 March 2022

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