Protocol

Study ID: 209668

Official Title of Study: Phase IIb Multi-Center, Randomised, Partial-Blind Parallel Cohort Study to Assess the Efficacy and Safety of Treatment with GSK3228836 in Participants with Chronic Hepatitis B Virus (B-Clear)

IND Identifier: 122685

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TITLE PAGE

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Protocol Number: 209668 / Amendment 02

Compound Number or Name: GSK3228836

Study Phase: PHASE 2B

Short Title: Phase 2b Study of GSK3228836 in Participants with Chronic Hepatitis B (B-Clear)

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: IND 122685

EudraCT number: 2020-001083-29

Approval Date: 23-Sep-2021

SPONSOR SIGNATORY

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The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 02	23-SEP-2021	TMF-13956480
Amendment 01	10-MAY-2021	TMF-11803132
Original Protocol	09-APR-2020	2019N420582_00

Amendment 02: 23-Sep-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary driver for this amendment was a request from a regulatory agency to include nucleos(t)ide analogue (NA) therapy initiation until hepatitis B flare could be ruled out (specifically for the patients who are not receiving NA therapy at baseline).

Text has also been included to allow additional interim analyses prior to the end of study (after all participants have completed treatment) to support asset development planning and decision making.

In addition, minor typographical errors and inconsistencies have been corrected and minor editorial changes have been made. Changes made to the text body have been made concurrently in the synopsis.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 6.5.1 NA Treatment during and after the End of the Study; Section 7.1.1 Liver Chemistry Monitoring and Stopping Criteria Table 6	Added text: For participants who are not receiving NA therapy at baseline, initiate NA therapy if ALT ≥3x ULN and bilirubin >1.5x ULN, as per Section 7.1.1 (Liver Chemistry Monitoring and Stopping Criteria). NA therapy may be subsequently discontinued if other tests (e.g., HBV DNA, HBsAg) rule out hepatitis B flare.	As per regulatory request in consideration of participant safety.
Section 9.5 Interim Analyses	Added text: Additional interim analyses may be conducted after the third interim (at which time all participants will have completed treatment and sponsor staff [as specified in the blinding plan] will be unblinded), to support development planning and decision making. If conducted, these analyses will be unblinded to the sponsor staff (as specified in the blinding plan) and referenced in the clinical study report.	To allow further review of the data prior to end of study (after all participants have completed treatment).

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Phase IIb Multi-Center, Randomised, Partial-Blind, Parallel Cohort Study to Assess the Efficacy and Safety of Treatment with GSK3228836 in Participants with Chronic Hepatitis B Virus (B-Clear)

Short Title: Phase IIb study of GSK3228836 in Participants with Chronic Hepatitis B (B-Clear)

Rationale:

Study 209668 is intended to evaluate if treatment with GSK3228836 can achieve sustained virologic response (SVR, HBsAg <lower limit of quantitation [LLOQ] and HBV DNA <LLOQ sustained for 24 weeks post-GSK3228836 treatment end) with a finite course of GSK3228836. In addition, the study will evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic properties of GSK3228836 in the four dosing regimens.

Key Objectives and Estimand/Endpoints:

Objectives	Estimand/Endpoints
Primary	
Efficacy: To assess the efficacy of the three dosing regimens of GSK3228836 in participants with CHB	Primary estimands supporting the primary objective are defined as: - **Population**: separate assessment for the following: • participants with CHB on stable nucleos(t)ide therapy • participants with CHB not currently on nucleos(t)ide therapy - **Variable**: Participants achieving sustained virologic response (SVR, described in Section 9.4.2) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. - **Treatments**: arms 1, 2, and 3. Estimation of the within-arm response rate. - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherance to GSK3228836 will be handled assuming they had not happened (hypothetical strategy). - **Population summary**: proportion of participants who achieve SVR for each treatment arm. The primary estimands for each sub-population is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events. A supplementary estimand is defined to support the primary objective: - the supplementary estimand is defined in the same way as the main estimand, except the assessment time frame for participants achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the actual end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

Objectives	Estimand/Endpoints
Secondary	
Efficacy: To assess the efficacy of GSK3228836 on biomarkers and virus-specific antibody responses	The estimands supporting this secondary objective are defined as follows: **- Population**: separate assessment for the following: • participants with CHB on stable nucleos(t)ide therapy • participants with CHB not currently on nucleos(t)ide therapy. **- Treatments**: arms 1-4. Estimation within each arm. - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication will be ignored (treatment policy strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy) **1) Categorical Variables**: - Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment. - Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log_{10} IU/mL) and in HBV DNA (e.g., <1, ≥1, ≥2, ≥3 log IU/mL) - ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN - HBe antibody (anti-HBeAg) levels - **Population summary:** proportion of participants in each category for each treatment arm. **2) Continuous Variables**: Actual values and change from baseline over time of HBsAg and HBV DNA and actual values and change from baseline of HBeAg levels; HBs antibody (anti-HBsAg) levels - **Population summary**: mean values and mean changes from baseline for each variable in each treatment arm **3) Time to Event Variable**: Time to ALT normalization in absence of rescue medication in participants with baseline ALT>ULN - **Population summary**: Turnbull's estimate for non-parametric estimation of time to ALT normalization in each treatment arm The group of estimands supporting this objective for each sub-population is the population summary for each variable in each treatment arm 1-4 regardless of completing IP, interruptions in IP or adherence to IP and regardless of rescue medication (except for ALT normalization which can only be achieved in the absence of rescue medication)
Efficacy: To compare the efficacy between 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of GSK3228836 treatment	The same definition as the primary estimand except treatments and population summary are defined as: -**Treatments**: arms 1, 2, and 3. Three treatment comparisons between: arms 1 & 2, arms 1 & 3, and arms 2 & 3 - **Population summary**: difference in proportion of participants who achieve SVR between treatment arms

Objectives	Estimand/Endpoints
	The group of estimands supporting this objective for each sub-population are the difference in each treatment comparisons in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.
Pharmacokinetics (PK): To characterize GSK3228836 and nucleos(t)ide PK in participants with CHB	• In a subset of participants with intensive PK sampling: Derived GSK3228836 and nucleos(t)ide plasma PK parameters including, but not limited to, area under the concentration-time curve (AUC), concentration at the end of the dosing interval ($C\tau$), maximum observed concentration (C_{max}), time of maximum observed concentration (t_{max}). • In all participants: $C\tau$ and terminal half-life ($t_{½}$) of GSK3228836.

Overall Design:

The study is a Phase 2b, multi-center, randomized, partial-blind, parallel cohort study to assess the efficacy and safety of treatment with GSK3228836 in two populations of patients with CHB (1) participants on stable nucleos(t)ide treatment and (2) participants not currently on nucleos(t)ide therapy.

For each population (participants on stable nucleos[t]ide therapy and participants not currently on nucleos(t)ide therapy), participants will be randomized into one of 4 parallel arms:

- 300 mg GSK3228836 once/week for 24 weeks (plus loading doses on Day 4 and Day 11);
- 300 mg GSK3228836 once/week for 12 weeks (plus loading doses on Day 4 and Day 11) followed by step-down in dose of 150 mg GSK3228836 once/week (plus placebo to match to maintain participant blinding) for 12 weeks;
- 300 mg GSK3228836 once/week for 12 weeks (plus loading doses on Day 4 and Day 11) followed by placebo once/week for 12 weeks;
- Placebo once/week for 12 weeks followed by 300 mg GSK3228836 once/week for 12 weeks (plus placebo loading doses to match on Day 4 and Day 11, no loading dose for GSK3228836 treatment)

Disclosure Statement:

This is a parallel group treatment study with 8 arms that is sponsor and participant blinded.

Number of Participants:

The study will plan to enrol approximately 440 participants.

In the case of a disruptive event impacting study treatment dosing, participation, and/or withdrawal, the study team may enroll additional participants to within 10% of the planned 440.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and after study personnel have confirmed that all eligibility criteria have been met. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

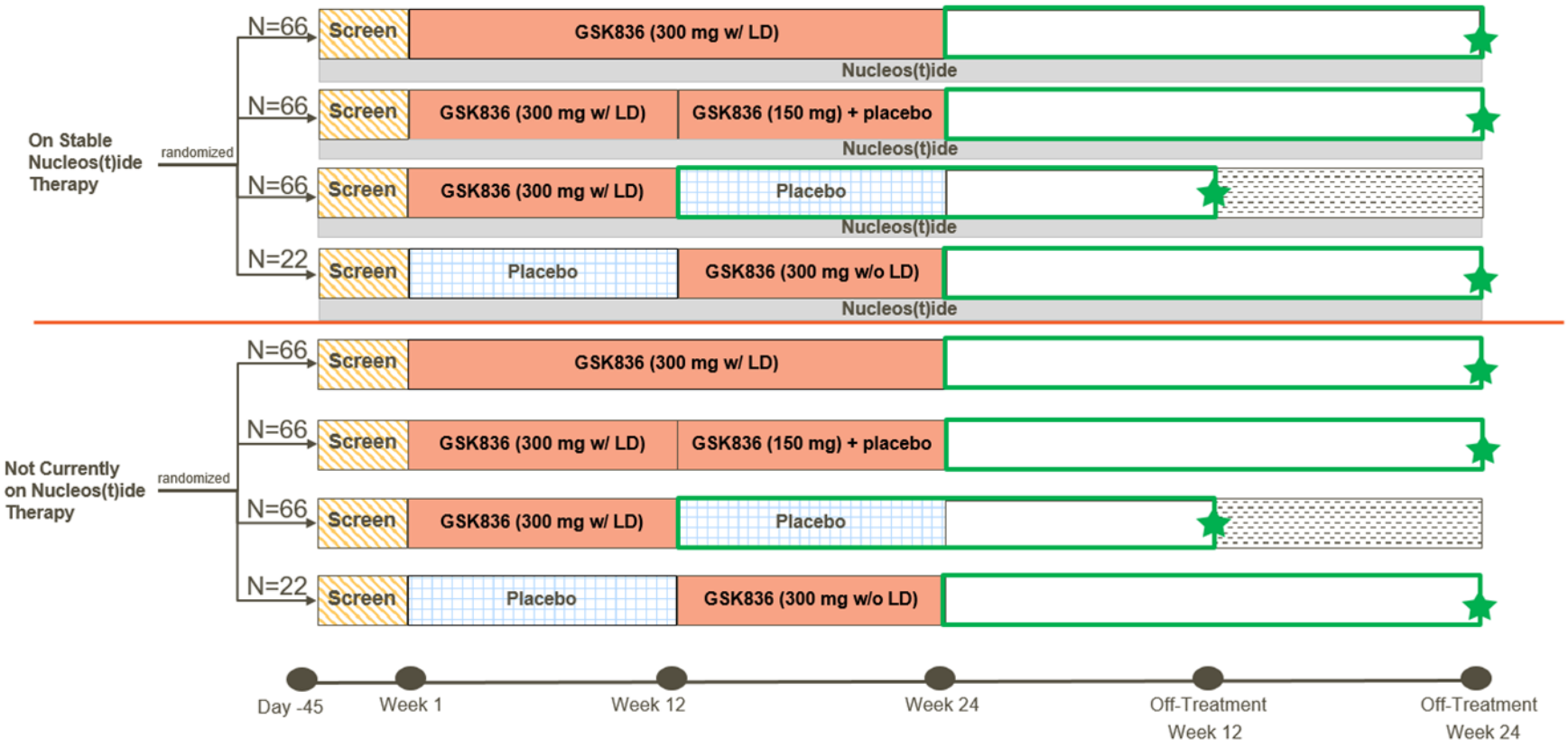
The total duration of the study, including screening, treatment, and post-treatment follow-up, is not expected to exceed 55 weeks for each participant.

- 45-day screening window. Eligible participants who fall out of the 45-day window may be re-screened at the discretion of the Investigator/site
- 24 weeks treatment with either GSK3228836 and/or placebo
- 24 weeks post treatment follow-up

There are no plans for group dose adjustments. Individual dose adjustments for safety are outlined in the monitoring/stopping criteria.

Data Monitoring or Other Committee: Yes

1.2. Schema


On Stable Nucleos(t)ide Therapy
randomized
N=66
Screen
GSK836 (300 mg w/ LD)
Nucleos(t)ide
N=66
Screen
GSK836 (300 mg w/ LD)
GSK836 (150 mg) + placebo
Nucleos(t)ide
N=66
Screen
GSK836 (300 mg w/ LD)
Placebo
Nucleos(t)ide
N=22
Screen
Placebo
GSK836 (300 mg w/o LD)
Nucleos(t)ide
Not Currently on Nucleos(t)ide Therapy
randomized
N=66
Screen
GSK836 (300 mg w/ LD)
N=66
Screen
GSK836 (300 mg w/ LD)
GSK836 (150 mg) + placebo
N=66
Screen
GSK836 (300 mg w/ LD)
Placebo
N=22
Screen
Placebo
GSK836 (300 mg w/o LD)
Day -45
Week 1
Week 12
Week 24
Off-Treatment Week 12
Off-Treatment Week 24
Note: planned N=approx. 440; In the case of a disruptive event impacting study treatment dosing/participation/withdrawal, the study team may enroll additional participants to within 10% of the planned N=440.
For GSK836 150 mg, a placebo injection is added to maintain participant blinding
GSK836, GSK3228836; LD, loading dose; w/, with; w/o, without
Follow-up period beyond primary endpoint, exploring durability of response; data to be included in end of study analyses
Primary endpoint analysis, sustained response for 24 weeks from end of planned GSK3228836 treatment

1.3. Schedule of Activities (SoA)

[China specific Schedule of Activities can be found in Appendix 7].

Table 1 Screening

ASSESSMENTS	
Informed Consent	X
Inclusion and exclusion criteria	X
Demography	X
Medical history (includes substance usage) and current medical conditions	X
Medication history and concomitant medication review	X
Full physical exam including height and weight	X
Vital signs	X
12-lead ECG	X
LABORATORY	
Serum hCG pregnancy test (women of child-bearing potential)	X
FSH/Estradiol (to confirm status of women of non-child-bearing potential)[1]	X
Hematology/Chemistry/Urinalysis	X
Urine ACR	X
PT, INR, aPTT	X
HIV, hepatitis D, and hepatitis C screen	X
Hepatitis B profile (HBsAg, HBV DNA, HBeAg)	X
Alpha-fetoprotein	X
APRI/Fibrosure	X
ANCA[2]	X
Total bile acid profile (as available)	X
Complement C3, C4, C5a, hsCRP, MCP-1, complement Bb, Ang-2	X

1. As appropriate to confirm menopause
2. With MPO-ANCA, PR3-ANCA if results are positive or border-line positive

Table 2 On Treatment Day 1 to Day 50

ASSESSMENTS[1]	**Day 1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
Window		±1 day			±3 days					
	Week 1	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
Randomization	X									
Study treatment dosing	X	X	X	X	X	X	X	X	X	X
Safety Assessments										
AE/SAE review	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Symptom directed exam	X						X			
Vital signs	X	X	X	X	X	X	X	X	X	X
Injection site reactions	X	X	X	X	X	X	X	X	X	X
Questionnaire (cell phone app, optional)	X									
Questionnaire (patient feedback on dosing regimen)	X									
Patient Reported Outcomes Questionnaires: HBQOL, EQ-5D	X									
Laboratory										
Pregnancy test (women of child bearing potential)[2]	X[2]						X			
Hematology[3] [includes platelet count and WBC]	X		X		X	X	X	X	X	X
PT, INR, aPTT	X						X			
Chemistry	X		X		X	X	X	X	X	X
Urinalysis	X		X		X	X	X	X	X	X
Urine ACR	X				X		X		X	
HBsAg and HBV DNA	X		X		X	X	X	X	X	X
Anti- HBsAg	X						X			
Anti-HBeAg	X						X			
HBeAg (only for participants HBeAg positive at screening)	X		X		X	X	X	X	X	X
HBV RNA, HBcrAg, and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)	X					X				X
Complement C3, Complement C4, hs-CRP, MCP-1	X				X		X		X	
Complement C5a, Complement factor Bb	X				X		X		X	
ANCA, Ang II	X						X			

ASSESSMENTS[1]	**Day 1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
Window		±1 day			±3 days					
	Week 1	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
PK	X		X		X	X	X	X	X	X
PBMC Collection for immunophenotyping[4]	X									
Soluble Protein (immunology)	X					X				X
PAXGene RNA for expression analysis in whole blood	X				X					
OPTIONAL: Genetics	X									
Archived Samples [serum; plasma]	X				X		X		X	

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM
2. A WOCBP must have both:
    a. A confirmed menstrual period prior to the first dose of study intervention; additional evaluation (e.g., amenorrhea in athletes, birth control) should also be considered
    b. AND a negative highly sensitive pregnancy test [urine or serum] within 24 hours before the first dose of study treatment
3. Hematology- platelet count to be analyzed at local laboratory prior to dose; hematology samples to be collected for central laboratory assessments in parallel
4. Only for selected sites able to transport to the analysis lab as specified in the SRM.

Table 3 On-Treatment: Day 57 to Day 162

Assessments[1]	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D120**	**D127**	**D134**	**D141**	**D148**	**D155**	**D162**
Window	± 3 days															
	W9	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**
Study treatment dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom directed exam	X				X				X				X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaire (cell phone app, optional)																X
Questionnaire (patient feedback on dosing regimen)																X
Laboratory																
Pregnancy test (women of child bearing potential)	X				X				X				X			
Hematology[2] [includes platelet count and WBC]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X				X				X				X			
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR	X		X		X		X		X		X		X		X	
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti- HBsAg	X				X				X				X			
Anti- HBeAg	X				X				X				X			
HBeAg (only for participants HBeAg positive at screening)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV RNA, HBcrAg, and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)				X				X				X				X
Complement C3, Complement C4, hs-CRP, MCP-1	X		X		X		X		X		X		X		X	

Assessments[1]	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D120**	**D127**	**D134**	**D141**	**D148**	**D155**	**D162**
Window	± 3 days															
	W9	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**
Complement C5a, Complement factor Bb	X		X		X		X		X		X		X		X	
ANCA, Ang II	X				X				X				X			
PK[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PBMC Collection for immunophenotyping[4]				X												X
Soluble protein (immunology)				X				X				X				X
PAXGene RNA for expression analysis in whole blood					X											
Archived Samples [serum; plasma]	X		X		X		X		X		X		X		X	

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM
2. Hematology- platelet count to be analyzed at local laboratory prior to dose; hematology samples to be collected for central laboratory assessments in parallel
3. In addition to the pre-dose PK sample, intensive PK may be collected for China, Japan, and country(ies) with participants of non-Asian heritage (TBD) see Table 8 for details of intensive PK sample collection
   a. Intensive PK (GSK3228836 and nucleos[t]ide) will be collected at 1 visit between Week 14 (inclusive) and Week 24 (inclusive), selected between the site and participant: post dose at 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 8 hr, 12 hr, 24 hr, 72 hr, and 168 hr [the site should make all attempts to align the 168 hr post-dose PK with the next scheduled visit's pre-dose PK, see Table 8 for more details]]
4. Only for selected sites able to transport to the analysis lab as specified in the SRM.

Table 4 Off-Treatment Follow-Up

Assessments[1]	**OT-Day 1**	**OT-Day 8**	**OT-Day 22**	**OT-Day 50**	**OT-Day 78**	**OT-Day 106**	**OT-Day 134**	**OT-Day 162**	**Early Termination**
Window	±3 Days		±10 Days						
	OT- W1	**OT-W2**	**OT-W4**	**OT-W8**	**OT-W12**	**OT-W16**	**OT-W20**	**OT-W24**	
Questionnaire									
Patient Reported Outcomes Questionnaire: HBQOL, EQ-5D								X	X
Safety Assessments									
AE/SAE review	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X
Symptom directed exam	X	X		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Laboratory									
Pregnancy test (women of child bearing potential)	X		X	X	X	X	X	X	X
Hematology[2] [includes platelet count and WBC]	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X		X		X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Urine ACR	X	X	X	X	X	X	X	X	X
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X
Anti- HBsAg	X	X	X	X	X	X	X	X	X
Anti- HBeAg	X	X	X	X	X	X	X	X	X
HBeAg (only for participants HBeAg positive at screening)	X	X	X	X	X	X	X	X	X
HBV RNA, HBcrAg, and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)	X		X		X		X	X	X
Complement C3, Complement C4, hs-CRP, MCP-1		X	X	X	X	X	X	X	X

Assessments[1]	**OT-Day 1**	**OT-Day 8**	**OT-Day 22**	**OT-Day 50**	**OT-Day 78**	**OT-Day 106**	**OT-Day 134**	**OT-Day 162**	**Early Termination**
Window	±3 Days		±10 Days						
	OT- W1	**OT-W2**	**OT-W4**	**OT-W8**	**OT-W12**	**OT-W16**	**OT-W20**	**OT-W24**	
Complement C5a, Complement factor Bb		X	X	X	X	X	X	X	X
ANCA, Ang II	X		X	X	X	X	X	X	X
PK	X	X	X	X	X	X	X	X	X
PBMC Collection for immunophenotyping[3]	X				X			X	X
Soluble Protein (immunology)	X		X		X		X	X	X
PAXGene RNA for expression analysis in whole blood	X				X			X	X
APRI/Fibrosure								X	X
Archived Samples [serum; plasma]	X	X	X	X	X	X	X	X	X

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM.

2. Hematology- platelet count analyzed at local laboratory is **optional** during the off-treatment period; hematology samples to be collected for central laboratory assessments (required; if local lab is being drawn, in parallel with local lab sample).
3. Only for selected sites able to transport to the analysis lab as specified in the SRM.

OT: off-treatment; the first off-treatment visit occurs 7 days after the last study treatment dose received, whether planned or last dose given after participant is withdrawn from study treatment (e.g., the planned first off-treatment visit occurs on Day 169, 7 days after the Day 162 visit; if participant is withdrawn from study treatment on Day 50, the first off-treatment visit occurs on Day 57)

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 2b study examining multiple dose administration of GSK3228836 in participants with CHB. This study will evaluate the efficacy, safety, and PK profile of GSK3228836 and provide a first look at differences between efficacy and/or durability of HBsAg suppression when GSK3228836 is given as 24 weeks treatment at 300 mg GSK3228836 with loading doses, 12 weeks treatment at 300 mg GSK3228836 with loading doses followed by 12 weeks treatment at a step-down dose of 150 mg GSK3228836, 12 weeks treatment at 300 mg GSK3228836 with loading doses, and 12 weeks placebo followed by 12 weeks treatment at 300 mg GSK3228836 without loading doses.

Data from this study will provide an assessment of the safety, tolerability, pharmacokinetic and pharmacodynamic outcomes of the different dosing regimens and identification of the optimal treatment regimen(s), thus supporting subsequent clinical studies.

2.2. Background

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, with only 9% of patients with Hepatitis B being treated. Viral hepatitis led to 1.34 million deaths and of these deaths, 66% were the results of complications of CHB infection [WHO, 2015].

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated liver disease, end-stage liver disease, hepatocellular carcinoma (HCC), or death. This goal can be achieved if HBV replication is suppressed in a sustained manner thereby decreasing the histological activity of CHB and reducing the risk of cirrhosis and HCC [Liaw, 2004; Feld, 2009]. In both HBeAg-positive and HBeAg negative CHB, the ultimate treatment endpoint is loss of detectable serum hepatitis B surface antigen (HBsAg) [Lok, 2009; EASL, 2012]. Loss of HBsAg is preceded by a robust immunological response to HBV infection resulting in sustained suppression of serum HBV deoxyribonucleic acid (DNA) and disease resolution.

First-line therapy for CHB is treatment with a nucleoside or nucleotide (nucleos(t)ide) analogue (NA). While these antiviral agents are effective in suppressing HBV replication in both HBeAg-positive and HBeAg-negative CHB, patients frequently relapse after treatment is discontinued, particularly if HBsAg loss was not achieved. Treatment with a pegylated interferon (PEG-interferon), of which 2 are available, is also approved for CHB [Lok, 2009; EASL, 2012] for a defined treatment duration (usually up to 48 weeks). Because of their frequent and sometimes severe side effects and high cost versus a small gain in treatment response, PEG-interferons are less frequently used than NAs. Unfortunately, with both the NAs and PEG-interferon, HBsAg loss and the subsequent development of antibodies to HBsAg is rarely achieved. Rates of HBsAg loss following

12 months of treatment with either a NA or PEG-interferon generally range from 0 to 3% in most studies [Lok, 2009; EASL, 2012]. Loss of HBeAg occurs more frequently following treatment with either the NAs or PEG-interferon, approximately 15 to 30% after 1 to 2 years of therapy, but off treatment durability is variable and questions remain as to whether virologic responses can be maintained over an extended follow-up period. Thus, most patients on treatment fail to achieve a sustained off-treatment virological response and require extended and often life-long therapy to suppress HBV DNA.

It has been proposed that the continued production of viral antigens by infected hepatocytes interferes with immune clearance of both the infected cells and circulating virus particles [Vanlandschoot, 2003]. In vitro studies with human peripheral blood mononuclear cells (PBMCs) have shown HBsAg impairs the functioning of dendritic cells and inhibits the activation of monocytes [Vanlandschoot, 2002; Op den Brouw, 2009]. Further, data suggest the production of vast excess of non-replication competent HBsAg (so called "sub-viral particles") likely functions as a decoy for host antibody responses. Most chronically infected patients produce antibody to HBsAg, but these can only be detected as immune complexes due to the vast excess of circulating antigen [Maruyama, 1993]. HBeAg is also thought to have a role in immune response evasion through down regulation of the innate immune system [Milich, 1998; Wu, 2009; Walsh, 2012]. As noted above, since loss of HBsAg expression is rarely achieved while loss of HBeAg expression occurs in a higher proportion of the patient population, HBsAg appears to be the main antagonist of immune clearance.

Should the viral antigens be instrumental in preventing clearance of persistent infection by the immune system, reducing the expression of these antigens, especially HBsAg, would be expected to permit reconstitution of an immune response against HBV [Boni, 2007; Boni, 2012; Bertoletti, 2013]. Support for this hypothesis is the observation that spontaneous seroconversion and resolution of chronic infection is most likely in patients that have lower serum HBsAg levels [Chen, 2012; Höner Zu Siederdissen, 2014]. Similarly, during treatment with NAs, patients with low HBsAg levels are more likely to lose HBsAg and seroconvert to anti-HBs antibody positive than patients with high HBsAg levels [Wursthorn, 2010; Jaroszewicz, 2011; Boni, 2012; Höner Zu Siederdissen, 2014]. A study to examine whether inhibition of HBsAg production for a finite duration would lead to sustained suppression of HBV has not been possible up to the present due to the lack of specific inhibitors of HBsAg.

GSK3228836, an antisense oligonucleotide, was designed to inhibit the synthesis of HBsAg without having a direct effect on covalently closed circular DNA or integrated HBV DNA. GSK3228836 directly targets all HBV mRNAs via Ribonuclease H (RNase H) mediated degradation, resulting in the reduction of viral proteins including HBsAg. GSK32288336 treatment permits examination of whether reduction of HBsAg allows resumption of a host immune response against HBV and infected cells and can induce HBsAg seroclearance.

Recently, a functional cure of CHB infection has been endorsed as the endpoint for new HBV therapies. Functional cure of CHB infection is defined as sustained seroclearance of HBsAg from serum (with or without anti-HBsAg seroconversion,) and undetectable HBV DNA in serum, after completion of a finite course of treatment [Lok, 2017].

Functional cure occurs in only a very small percentage of patients on NA therapy alone (approx. 3% per annum), meaning that patients frequently relapse once they are taken off treatment [Lok, 2017]. The high rate of relapse in these patients is hypothesised to be due to their inability to raise an effective immune response to the virus in the presence of high circulating levels of HBsAg, which continues to be produced by infected hepatocytes, even in the absence of ongoing viral replication. The present study will investigate whether pharmacological suppression of HBV antigens up to 24 weeks of treatment by GSK3228836 will allow patients to achieve functional cure.

2.3. Benefit/Risk Assessment

More detailed information about the identified and potential benefits and risks and expected adverse events of GSK3228836 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Risks are summarized in Table 5. Additional withdrawal/stopping criteria for liver chemistry monitoring, drug induced vascular injury (DIVI), hematology, renal function, and PK are discussed in Section 7. Planned dose adjustments for individuals for safety are outlined in Section 6.6.

Table 5 Summary of Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3228836]		
Nonclinical Risks: Drug Induced Vascular Inflammation and Complement Activation	Inflammatory and immune changes are recognized as a class effect of antisense oligonucleotide (ASOs). Vasculitis and/or perivascular inflammation has been described in monkey studies with many if not most ASOs. This effect has not been observed in clinical studies with GSK3228836 to date.	**Laboratory Evaluations**: Inclusion of biomarker panels to look for inflammatory and immune activation that would be expected to accompany vascular injury **Stopping Criteria:** Proposed Monitoring Schedule and Stopping Rules for Drug Induced Vascular Injury and Complement Activation (see Section 7.1.2)
Clinical Risks:		
Drug induced liver injury / ALT Flares	The liver is a site of accumulation of antisense oligonucleotides. Liver findings in nonclinical studies of GSK3228836 were generally limited to mild hepatic enzyme elevations associated with hepatic vacuolation without concomitant histologic evidence of degeneration in mice, consistent with findings noted with other 2'-methoxyethyl (MOE) ASOs. Review of the available clinical data indicates liver enzymes are increased on treatment with ASOs in a low percentage of patients compared to placebo. ALT elevations (defined as ALT ≥ 2X ULN) associated with HBsAg reductions were observed in 8 out of 18 treatment-naïve participants in the ISIS 505358-CS3 study (150 mg GSK3228836, N=6; 300 mg GSK3228836, N=12). Among the 8 participants with ALT flares, 6 achieved >1 log HBsAg reduction, another 2 had >0.5 log HBsAg reduction.	**Laboratory Evaluations:** hepatic enzyme monitoring as presented in Table 6 **Stopping Criteria:** ALT flares are expected in the study population. Monitoring and stopping criteria are presented in Section 7.1.1

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 GSK3228836, there were incidences of both types in a 39-week study. Thrombocytopenia was not reported in the clinical studies with GSK3228836 (ISIS 505358-CS1 and ISIS 505358-CS3)	**Laboratory Evaluations:** platelet count **Stopping Criteria:** monitoring and stopping criteria are presented in Section 7.1.3
Drug-Induced Kidney Injury	Glomerulonephritis has been reported with ASOs and is thought to be a result of the proinflammatory effect of ASOs. No adverse events related to renal function were reported in Study ISIS 505358-CS3	**Laboratory Evaluations:** Serum creatinine, eGFR, urinalysis with microscopy and ACR assessed per the SoA tables **Stopping Criteria:** Monitoring Schedule and Stopping Rules are presented in Section 7.1.4
Injection site reactions	Injection site reactions have been reported with ASOs, and reported in clinical studies with GSK3228836 (ISIS 505358-CS1 and ISIS 505358-CS3). Injection site reactions were the most common study treatment-related AEs reported and were Grade 1 (mild) and Grade 2 (moderate) in severity.	**Evaluations:** Participants are assessed for injection site reactions at all visits during the on-treatment period. In order to minimize the risk of injection site reaction (ISR), 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.

2.3.1.1. Regarding Coronavirus Disease 2019 (COVID-19)

In addition to the study related risks listed in Table 5, it should be noted that COVID-19 is a risk for everyone. The magnitude of the risk depends on the prevalence in the population, frequency, duration and closeness of contact with other people, use of protective measures, age, ethnicity, sex and co-morbidities including medications.

Currently, there is no evidence that patients with chronic HBV have increased susceptibility to severe acute respiratory syndrome coronavirus 2 virus strain (SARS-CoV-2) infection. Patients with uncomplicated viral hepatitis (i.e., without cirrhosis, or history of transplantation or current immunosuppressant use) don't appear to be over-represented in hospitalized or intensive care unit cases of COVID-19, and therefore viral hepatitis isn't considered a risk factor for a more severe course of COVID-19 [Fix, 2020; Boettler, 2020].

The actual risk of COVID-19 will vary by country and region, so study participants should follow any national or local hospital restrictions, as well as specific recommendations from their healthcare providers.

2.3.2. Benefit Assessment

Treatment of CHB with nucleos(t)ide analogues has been effective in reducing the long-term complications of CHB, but evidence is emerging that HBsAg loss is associated with lower rates of hepatocellular carcinoma [Kim, 2014; Yip, 2016]. Even patients who achieve complete viral suppression experience significantly lower rates of hepatocellular carcinoma if they are able to achieve HBsAg loss. Thus, there is a need in patients with CHB for a finite treatment that allows them to achieve immune control of their infection (functional cure, defined as HBsAg loss with HBV DNA suppression), removing the need for lifelong therapy and to improve long term disease outcomes, particularly development of hepatocellular carcinoma.

GSK3228836 demonstrated target engagement in CHB patients who were not on treatment and in CHB patients on stable NA therapy. Overall, continued clinical development of GSK3228836 is supported by the results from the completed study ISIS 505358-CS3. It is not known if there will be any direct therapeutic benefit to the CHB population that will be included in this study. However, their participation could potentially contribute to the development of an improved treatment for patients with CHB.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with GSK3228836 and from COVID-19 are balanced by the anticipated benefits that may be afforded to participants with CHB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Estimand/Endpoints
Primary	
Efficacy: To assess the efficacy of the three dosing regimens of GSK3228836 in participants with CHB	Primary estimands supporting the primary objective are defined as: - **Population**: separate assessment for the following: • participants with CHB on stable nucleos(t)ide therapy • participants with CHB not currently on nucleos(t)ide therapy - **Variable**: Participants achieving sustained virologic response (SVR, described in Section 9.4.2) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. - **Treatments**: arms 1, 2, and 3. Estimation of the within-arm response rate. - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherance to GSK3228836 will be handled assuming they had not happened (hypothetical strategy). - **Population summary**: proportion of participants who achieve SVR for each treatment arm. The primary estimands for each sub-population is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events. A supplementary estimand is defined to support the primary objective: - the supplementary estimand is defined in the same way as the main estimand, except the assessment time frame for participants achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the actual end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

Objectives	Estimand/Endpoints
Secondary	
Efficacy: To assess the efficacy of GSK3228836 on biomarkers and virus-specific antibody responses	The estimands supporting this secondary objective are defined as follows: **- Population**: separate assessment for the following: • participants with CHB on stable nucleos(t)ide therapy • participants with CHB not currently on nucleos(t)ide therapy. **- Treatments**: arms 1-4. Estimation within each arm. - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication will be ignored (treatment policy strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy) **2) Categorical Variables**: - Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment. - Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log_{10} IU/mL) and in HBV DNA (e.g., <1, ≥1, ≥2, ≥3 log IU/mL) - ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN - HBe antibody (anti-HBeAg) levels - **Population summary:** proportion of participants in each category for each treatment arm. **2) Continuous Variables**: Actual values and change from baseline over time of HBsAg and HBV DNA and actual values and change from baseline of HBeAg levels; HBs antibody (anti-HBsAg) levels - **Population summary**: mean values and mean changes from baseline for each variable in each treatment arm **3) Time to Event Variable**: Time to ALT normalization in absence of rescue medication in participants with baseline ALT>ULN - **Population summary**: Turnbull's estimate for non-parametric estimation of time to ALT normalization in each treatment arm The group of estimands supporting this objective for each sub-population is the population summary for each variable in each treatment arm 1-4 regardless of completing IP, interruptions in IP or adherence to IP and regardless of rescue medication (except for ALT normalization which can only be achieved in the absence of rescue medication)

Objectives	Estimand/Endpoints
Efficacy: To compare the efficacy between 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of GSK3228836 treatment	The same definition as the primary estimand except treatments and population summary are defined as: -**Treatments**: arms 1, 2, and 3. Three treatment comparisons between: arms 1 & 2, arms 1 & 3, and arms 2 & 3 - **Population summary**: difference in proportion of participants who achieve SVR between treatment arms The group of estimands supporting this objective for each sub-population are the difference in each treatment comparisons in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.
Pharmacokinetics (PK): To characterize GSK3228836 and nucleos(t)ide PK in participants with CHB	• In a subset of participants with intensive PK sampling: Derived GSK3228836 and nucleos(t)ide plasma PK parameters including, but not limited to, area under the concentration-time curve (AUC), concentration at the end of the dosing interval ($C\tau$), maximum observed concentration (C_{max}), time of maximum observed concentration (t_{max}). • In all participants: $C\tau$ and terminal half-life ($t_{½}$) of GSK3228836.
Safety	
Safety: To assess the safety and tolerability of GSK3228836 when dosed for 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks duration in participants with CHB	Clinical assessments including, but not limited to vital signs, laboratory measurements and adverse events
Exploratory	
PK-PD relationships: To evaluate PK-efficacy relationship and PK-safety relationship	Exploratory graphical analyses will be initially performed for efficacy (e.g., HBsAg) and safety endpoints. If a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modelling will be conducted using nonlinear mixed effect methods. The model will assess the effect of various factors (covariates) of the modelled efficacy or safety endpoints. Relevant PK-PD model endpoints for example: • apparent clearance • apparent volume of distribution • IC50 • random variability
Efficacy: To compare the efficacy between 12 weeks of GSK3228836 treatment with a loading dose or without a loading dose	The same definition as the primary Estimand except treatments and population summary are defined as: - **Treatments**: arm 3 & 4. Treatment comparison between arms 3&4. - **Population summary**: difference in proportion of participants who achieve SVR between treatment arms 3 & 4. The group of estimands supporting this objective for each sub-

Objectives	Estimand/Endpoints
	population are the differences between arms 3 & 4 in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.
Efficacy: To assess the pharmacodynamic effect of GSK3228836 on exploratory viral biomarkers	HBV core related antigen (HBcrAg), HBV RNA
Virology: To assess the effect of genotype/phenotype and presence of baseline polymorphisms within the GSK3228836 binding site to assess the effect on treatment response. To assess the emergence of mutations within the GSK binding site, and elsewhere in the hepatitis B genome, during and after treatment.	Sequencing of the viral HBV DNA and/or HBV RNA prior to treatment, during treatment and post treatment visits
Immunology: To assess the effect of 12 weeks, 12 weeks + 12 weeks step-down or 24 weeks treatment with GSK3228836 on immunological biomarkers. To describe the relationship(s) between virology biomarkers, including but not limited to HBsAg, and immunological biomarkers.	Laboratory measurements of and correlation between the following • Virological biomarkers, as determined by (but not limited to) specific viral parameters (HBeAg, HBV DNA, HBV RNA, HBcrAg). • Soluble immunological biomarkers, as determined by (but not limited to) levels of circulating cytokines and chemokines. • Markers of immune cell function, as measured by (but not limited to) relative frequencies of immune cell subsets among PBMCs, activation status as determined by phenotyping and gene expression patterns, and functional assays including HBV-specific cytokine and/or antibody production
Patient Reported Outcomes: To assess changes from baseline in patient reported outcomes following 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of treatment with GSK3228836.	Change from baseline of HBQOL and EQ-5D.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, multi-center, randomized, partial-blind [Sponsor and Participant blinded], study to assess efficacy and safety of treatment with GSK3228836 in two populations of patients with CHB (1) participants on stable nucleos(t)ide treatment and (2) participants not currently on nucleos(t)ide therapy.

Both populations of patients with CHB will be randomized into one of 4 parallel arms:

- 300 mg GSK3228836 once/week for 24 weeks (plus loading dose of 300 mg GSK3228836 on Day 4 and Day 11);
- 300 mg GSK3228836 once/week for 12 weeks (plus loading dose of 300 mg GSK3228836 on Day 4 and Day 11) followed by step-down in dose of 150 mg (plus placebo to match to maintain participant blinding) GSK3228836 once/week for 12 weeks;
- 300 mg GSK3228836 once/week for 12 weeks (plus loading dose of 300 mg GSK3228836 on Day 4 and Day 11) followed by placebo once/week for 12 weeks;
- Placebo once/week for 12 weeks followed by 300 mg GSK3228836 once/week for 12 weeks (plus placebo loading doses to match on Day 4 and Day 11, no loading dose for GSK3228836 treatment)

After the 24 weeks of dosing with GSK3228836 or placebo, there will be a post-treatment follow-up period of 24 weeks.

Populations will be stratified based on HBsAg level (HBsAg ≤3 log IU/mL and >3 log IU/mL) and whether participants are HBeAg positive or negative.

The study is a partially blinded study where participants will be blinded to the study treatment. The investigators, site staffs and pharmacist will be unblinded. GSK and contract research organization (CRO) team members will be blinded to participants' study treatment and any potentially unblinding information, unless specified otherwise in the study blinding management plan (e.g., unblinded site monitors).

4.2. Scientific Rationale for Study Design

In a previous clinical study (ISIS 505358-CS3), 7 of 12 (58%) of treatment-naïve participants dosed with 300 mg GSK3228836 over 4 weeks experienced a ≥0.5 $\log_{10}$ reduction in HBsAg by Day 29. Two treatment-naïve participants dosed with 300 mg GSK3228836 experienced HBsAg loss that persisted for 102 and 28 days, respectively, before the HBsAg became detectable again.

In participants on stable nucleos(t)ide analogue therapy, 3 of 5 (60%) participants treated with 300 mg GSK3228836 achieved HBsAg reductions >3 log10 IU/mL. Two of five participants (40%) treated with 300 mg GSK3228836 achieved HBsAg <LLOQ (0.05 IU/mL). One participant reached HBsAg levels <LLOQ on Day 23, but this was not

sustained. HBsAg was detectable on the Day 85 and Day 113 visits. One participant had HBsAg <LLOQ on Day 36 and remained <LLOQ as of the Day 85 visit.

The proposed Phase 2b study (209668) will evaluate whether up to 24 weeks treatment with GSK3228836 results in a clinically meaningful rate of sustained virologic response (SVR, HBsAg <LLOQ and HBV DNA <LLOQ) with a finite course of GSK3228836. The study will evaluate the efficacy, safety, tolerability, pharmacokinetic and pharmacodynamic properties of GSK3228836 when dosed as part of four different dosing regimens.

4.2.1. Rationale for Study Blinding

A partial blind study (participant and sponsor blinded, site staff unblinded) was chosen because there is a high probability that the PI and site staff could infer treatment assignment due to:

- Differences in the injection force due to the viscosity of GSK3228836 versus placebo saline.
    a. GSK3228836 is much more viscous than placebo saline and the administrating site staff may be able to infer treatment based on the differences in pressure exerted to administer the dose.
- Color difference of GSK3228836 versus placebo
    - Syringes will be wrapped in a colored transparent tape to prevent unblinding of the participant.
- Laboratory results (e.g., platelets, ALT, HBV DNA and HBsAg) needed in the course of participant treatment and/or safety management
    a. Platelet decreases and thrombocytopenia have been reported with ASOs. In this study thrombocytopenia is an AE of special interest. For safety management of the participants, the platelet counts cannot be blinded.

    b. ALT increases are expected to be seen during the course of treatment with GSK3228836. In the previous ISIS 505358-CS3 study, where participants received up to 4 weeks of 300 mg GSK3228836 treatment, 33% of treatment-naïve participants had increase in ALT ≥3x ULN, not associated with other chemistry changes (e.g., bilirubin, INR). In order for the investigator to better ascertain the etiology of an ALT increase (e.g., drug-induced liver injury vs therapeutic flare vs nucleos(t)ide treatment failure ALT increase), virology data are required.

    c. HBV DNA results are needed to evaluate whether to initiate nucleos(t)ide treatment in the event of a sub-optimal response or virological failure in response to GSK3228836. Initiation of nucleos(t)ides should reduce the risk of development of resistance to GSK3228836.

Participants will be kept blinded to decrease reporting bias and to decrease risk of missed visits during the placebo part of the study. The Sponsor will remain blinded to minimize bias (unless specified otherwise in the study blinding management plan (e.g., unblinded site monitors). The primary endpoint assessments (HBsAg, HBV DNA) are objective

laboratory measurements and therefore the unblinding of the site staff will not compromise the assessment of the primary endpoint of the study.

4.2.2. Rationale for Placebo-First Arm

Inflammatory and immune changes are recognized as a class effect of ASOs. Vasculitis and/or perivascular inflammation has been described in pre-clinical monkey studies with many ASOs, including pre-clinical monkey studies with GSK3228836. However, this effect has not been observed in clinical studies with GSK3228836 to date.

As part of the safety monitoring, inclusion of biomarker panels to look for inflammatory and immune activation that would be expected to accompany vascular injury have been included. The biomarkers being utilized to monitor for inflammatory and immune activation (e.g., complement factors C3, C4, C5a, Bb; ANCA; MCP-1) are exploratory in nature with little to no literature around normal values/behaviors in chronic hepatitis B patients. The placebo-first arm (placebo treatment for 12 weeks, 300 mg GSK3228836, then off-treatment follow-up for 24 weeks) will be used as a comparator for these exploratory safety analyses.

The placebo-first arm (placebo treatment for 12 weeks, 300 mg GSK3228836 for 12 weeks, then off-treatment follow-up for 24 weeks) will also provide an assessment for loading versus non-loading dose. Participants in the placebo-first arm will not be receiving loading dose when starting their 12 weeks 300 mg GSK3228836 treatment, and efficacy results (Week 13-24) may be compared with participants being treated for 12 weeks of 300 mg GSK3228836 with loading dose (Week 1-12).

The comparisons/assessments for the placebo-first arm are not statistically powered.

4.2.3. Participant Input into Design

A small group of patients with CHB were asked to review an example informed consent form for the 209668 study. The patients provided feedback for more clarity in the informed consent form regarding the purpose of the study and optional assessments (e.g. biomarkers), mode of administration of GSK3228836, the study burden in both terms of visit schedule and duration of visit. Efforts to reduce the burden of visits were encouraged. The input from the patients will be incorporated into the Informed Consent Form. The study team reviewed the blood collection timepoints and made changes to balance participant burden with the data/timepoints needed for safety and efficacy analyses.

Due to the feedback from patients that the number of visits may be challenging (weekly visits to the clinic/hospital), the study team are working with countries/sites to provide an option where participants may use a centralised home nursing provider. The home nursing providers will go to the participant, decreasing the number of times the participant must travel to/from the clinic/hospital. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM.

4.3. Justification for Dose

Dose Levels, Frequency and Duration

Weekly dosing of GSK3228836 has been evaluated over a four-week dosing duration in both healthy volunteers (ISIS 505358-CS1 study) and in participants with CHB (ISIS 505358-CS3 study). In both studies, GSK3228836 was administered subcutaneously on Study Day 1, 4, 8, 11, 15, and 22. The loading schedule (i.e., loading doses) in Week 1 (Day 4) and Week 2 (Day 11) were included in order to accelerate the achievement of steady state concentration in the liver to increase the likelihood of observing anti-HBV activity during a short treatment duration. In study 209668, a study arm will be included to explore placebo for 12 weeks followed by weekly dosing of GSK3228836 300 mg for 12 weeks without the loading doses (see below).

To date, the highest dose of GSK3228836 evaluated was 2700 mg over 4 weeks (450 mg per injection including loading doses; n=3) in healthy volunteers, and 1800 mg over 4 weeks (300 mg per injection including loading doses; n=18) in participants with CHB. In treatment-naïve participants with CHB dosed with 300 mg per injection in ISIS 505358-CS3 study, continuous HBsAg declines were observed in many participants during GSK3228836 treatment, with two participants achieving HBsAg seroclearance that persisted for 102 and 28 days, respectively. In participants who achieved HBsAg <LLOQ, HBsAg subsequently became detectable after discontinuation of GSK3228836 dosing. Moreover, many participants had declining HBsAg levels that hadn't plateaued by the end of treatment.

Similar responses were observed in participants in Study ISIS 505358-CS3 on stable NA therapy. Three of 5 GSK3228836-treated participants (60%) achieved HBsAg reductions >3 log10 IU/mL. Two of five participants (40%) treated with 300 mg GSK3228836 achieved HBsAg <LLOQ (0.05 IU/mL). One participant reached HBsAg levels <LLOQ on Day 23, but this was not sustained. HBsAg was detectable on the Day 85 and Day 113 visits. One participant had HBsAg <LLOQ on Day 36 and remained <LLOQ as of the Day 85 visit. Taken together, the data suggest that a longer duration of GSK3228836 therapy may be required to both increase the rate of seroclearance and to achieve sustained seroclearance.

In study 209668, 2 different treatment durations (12 weeks and 24 weeks) will be studied to assess differences in the efficacy endpoints (e.g., proportion of participants achieving seroclearance, durability of response) with GSK3228836 in two populations of patients with CHB:

(1) participants receiving stable nucleos(t)ide treatment and

(2) participants not currently receiving nucleos(t)ide therapy.

Study 209668 will also explore the impact on efficacy and safety of decreasing overall exposure to GSK3228836 by administrating a step-down dose of 150 mg GSK3228836 for 12 weeks after an initial 12 weeks of 300 mg GSK3228836 dose. In each population of patients with CHB (participants receiving stable nucleos[t]ide treatment and

participants not currently receiving nucleos[t]ide therapy), four different treatment regimens of GSK3228836 will be studied in study 209668:

- 300 mg GSK3228836 once/week for 24 weeks (plus loading doses on Day 4 and Day 11);
- 300 mg GSK3228836 once/week for 12 weeks weeks (plus loading doses on Day 4 and Day 11) followed by a step-down dose of 150 mg GSK3228836 once/week (plus placebo to match to maintain participant blinding) for 12;
- 300 mg GSK3228836 once/week for 12 weeks (plus loading doses on Day 4 and Day 11) followed by placebo once/week for 12 weeks;
- Placebo once/week for 12 weeks followed by 300 mg GSK3228836 once/week for 12 weeks (placebo loading doses to match on Day 4 and Day 11, no loading dose for GSK3228836 treatment)

Co-administration of GSK3228836 and Nucleos(t)ide Analogues

GSK3228836 is unlikely to be a victim or perpetrator of drug-drug interactions when administered with nucleos(t)ide analogues due to their divergent absorption, distribution, metabolism, and excretion pathways.

Drug-drug interactions with GSK3228836 as victim:

Upon entry into the system circulation, GSK3228836 rapidly becomes highly bound (approximately 95%) to serum proteins and is then rapidly distributed to tissues. GSK3228836 enters hepatic cells through target-mediated endocytosis and enters renal cells through micropinocytosis [Geary, 2008; Bennett, 2010]. GSK3228836 is eliminated primarily via nucleolytic degradation by endogenous endonucleases [Geary, 2008]. None of these processes is inhibited or induced by small-molecule drugs including nucleos(t)ide analogues (e.g. tenofovir, entecavir, lamivudine, adefovir and telbivudine).

In Cohorts 1-3 of the ISIS 505358-CS3 study, treatment-naïve participants were started on tenofovir after treatment ended; in Cohort 4, where participants were nucleos(t)ide experienced, the majority of participants entered the study on entecavir. Clinical data from this study suggest that co-administration of entecavir is unlikely to impact plasma PK of GSK3228836. GSK3228836 was co-administered with entecavir throughout the treatment period in 4 participants in Cohort 4 while administered alone in 18 participants in Cohorts 1 to 3. GSK3228836 plasma concentration was comparable with entecavir (n=4) and without entecavir (n=18). Dose normalization was applied to Cohort 1 as 150 mg of GSK3228836 was administered in Cohort 1 as compared to 300 mg in Cohorts 2 to 4.

Drug-drug interactions with GSK3228836 as perpetrator:

Tenofovir, entecavir, and other nucleos(t)ide analogues circulated in the blood stream with little binding to serum proteins [Bristol-Myers Squibb, 2018; Gilead, 2018]. Tenofovir, entecavir, lamivudine, adefovir and telbivudine are predominantly renally eliminated from systemic circulation [Epivir, 2002; Kearney, 2004; Hepsera, 2012; Tyzeka, 2013; Entecavir, 2015; Bristol-Myers Squibb, 2018; Gilead, 2018]. These 5

drugs undergo a combination of glomerular filtration and tubular secretion, which have been reported to be mediated by one or more of the following transporters: the organic anion transporter (OAT) 1, OAT3, the organic cation transporter (OCT) 1, and OCT2 [Cihlar, 2001; Cihlar, 2004; Servais, 2006; Uwai, 2007; Minuesa, 2009; Yanxiao, 2011; Xu, 2013]. It has been shown that 2'-MOE ASO is neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2 [Yu, 2016; Shemesh, 2017]. Therefore, although GSK3228836 was shown to be extensively distributed into the kidney in non-clinical studies, it is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir, telbivudine, or other nucleos(t)ide analogues.

Clinical data from ISIS 505358-CS3 suggest that co-administration of GSK3228836 is unlikely to impact efficacy and safety profiles. Given the long plasma and tissue half-life of GSK3228836 (approximately 3 weeks), there is a period of at least several weeks during which there was a substantial presence of both drugs in the plasma, liver and other tissues. Potent reduction of HBV DNA was observed following initiation of tenofovir in all participants. There were no obvious differences in tenofovir potency and efficacy in participants who received 150 mg of GSK3228836 (Cohort 1), 300 mg of GSK3228836 (Cohorts 2 and 3), and placebo (no GSK3228836). There were no adverse event or clinical laboratory results that may indicate a change in tenofovir safety profile due to drug-drug interaction with GSK3228836.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

AGE
1. At least 18 years of age at the time of signing the informed consent [if country/site age requirements for consent differ, the more stringent (e.g., higher age) restriction will be required for that country/site].
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants who have documented chronic HBV infection ≥6 months prior to screening AND a. Not currently on nucleos(t)ide analogue therapy population defined as participants who never received HBV treatment (treatment naïve) OR must have ended nucleos(t)ide therapy at least 6 months prior to the

screening visit

b. OR Currently receiving stable nucleos(t)ide analogue therapy population defined as no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study

3. Plasma or serum HBsAg concentration >100 IU/mL

4. Plasma or serum HBV DNA concentration

a. Participants not currently on nucleos(t)ide analogue therapy, plasma or serum HBV DNA >2000 IU/mL

b. Participants who are receiving stable nucleos(t)ide analogue therapy must be adequately suppressed, defined as plasma or serum HBV DNA <90 IU/mL

5. Alanine Transaminase (ALT)

a. ALT for treatment naïve participants and for participants who are not currently receiving treatment

i. ALT <3 X ULN will be included initially

1. If agreed by the IDMC after review of safety data, the ALT inclusion criteria may be expanded to include participants with ALT <5 X ULN

b. ALT ≤2 X ULN for participants who are receiving stable nucleos(t)ide analogue therapy

SEX

6. Male and/or Female

a. A male participant is eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study treatment

i. Refrain from donating sperm

ii. AND 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

1. 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. If she is not pregnant or breastfeeding

ii. AND at least one of the following conditions applies:

1. Is not a woman of childbearing potential (WOCBP)

2. OR is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency during the intervention period and for at least 90 days after the last dose of study treatment

iii. A WOCBP must have both

1. A confirmed menstrual period prior to the first dose of study intervention [additional evaluation (e.g., amenorrhea in athletes, birth control) should also be considered]

2. AND a negative highly sensitive pregnancy test [urine or serum] within 24 hours before the first dose of study treatment

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

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

INFORMED CONSENT

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

5.2. Exclusion Criteria

MEDICAL CONDITIONS

1. Clinically significant abnormalities, aside from chronic HBV infection in medical history (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, uncontrolled diabetes, bleeding diathesis or coagulopathy) or physical examination
2. Co-infection with:
    a. Current or past history of Hepatitis C virus (HCV)
    b. Human immunodeficiency virus (HIV)
    c. Hepatitis D virus (HDV)
3. 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
        i. If only one parameter (APRI or FibroSure/FibroTest) result is positive, a discussion with the Medical Monitor is required before inclusion in study is permitted
    b. Regardless of APRI of Fibrosure/FibroTest score, if the participant meets one of the following historical criteria, they will be excluded from the study
        i. Liver biopsy (i.e., Metavir Score F4)
        ii. Liver stiffness >12 kPa
4. 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
5. 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.
6. 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)
7. History of extrahepatic disorders possibly related to HBV immune conditions (e.g., nephrotic syndrome, any type of glomerulonephritis, polyarteritis nodosa, cryoglobulinaemia, uncontrolled hypertension)
8. Positive (or borderline positive) ANCA at screening:
    a. Participants that meet this criteria may be considered for inclusion in the study following:
        i. Analysis of MPO-ANCA [pANCA] and PR3-ANCA [cANCA] AND
        ii. A discussion with the Medical Monitor to review participant's complete medical history to ensure no past history or current manifestations of a

vasculitic/inflammatory/auto-immune condition

9. Low C3 at screening AND evidence of past history or current manifestations of vasculitic/inflammatory/auto-immune conditions
    a. All participants with low C3 at screening should have their medical history discussed with the Medical Monitor prior to enrolment
10. 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
        i. 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

PRIOR/CONCOMITANT THERAPY

11. Currently taking, or took within 3 months of screening, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks) or topical/inhaled steroid use.
12. Participants for whom immunosuppressive treatment is not advised, including therapeutic doses of steroids, will be excluded
13. Currently taking, or took within 12 months of screening, any interferon-containing therapy.
14. Participants requiring anti-coagulation therapies (for example warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel)

PRIOR/CONCOMITANT THERAPY

15. 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).
16. Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing day

DIAGNOSTIC ASSESSMENTS

17. Fridericia's QT correction formula (QTcF) ≥450 msec (if single electrocardiogram [ECG] at screening shows QTcF ≥450 msec, a mean of triplicate measurements should be used to confirm that participant meets exclusion criterion).
18. 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 CKD-EPI formula (for Japan, JSN-CKDI equation).
c. INR >1.25
d. Platelet count <140 X 10^9/L
e. Total bilirubin >1.25 x ULN
    i. For participants with benign unconjugated hyperbilirubinemia with total bilirubin >1.25 x ULN, discussion for inclusion to the study is required with the Medical Monitor
f. Urine albumin to creatinine ratio (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
    i. In cases where participants have low urine albumin and low urine creatinine levels resulting in a urine ACR calculation ≥0.03 mg/mg (or ≥30 mg/g), the investigator should confirm that the participant does not have a history of diabetes, hypertension or other risk factors that may affect renal function and discuss with the Medical Monitor, or designee

OTHER EXCLUSIONS
19. History of/sensitivity to GSK3228836 or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation

5.3. Lifestyle Considerations

5.3.1. Alcohol and Tobacco

During each dosing session, participants will abstain from alcohol for 24 hours before the start of each scheduled clinic visit until after they leave the clinic.

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.

5.3.2. Activity

Participants will abstain from strenuous exercise for 48 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 not be rescreened unless discussed and agreed with the Medical Monitor. Individuals who fall out of the screening window, may be rescreened at the discretion of the investigator and site.

5.5. Additional Participant Enrollment

The planned number of participants will be approximately 440.

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.

The study may enrol additional participants to within 10% of the planned 440 participants to support a sufficient safety database.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Study Treatment

Study Treatment		
Product Name:	GSK3228836	Placebo
Formulation Description:	Clear colorless to slightly yellow solution	Clear colorless solution
Dosage Form:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	150mg/mL; 1.0mL nominal volume per vial (minimal overfill per vial)	Placebo
Route/Administration/Duration:	SC, multiple (once weekly, up to 168 days, plus loading doses)	SC, multiple (once weekly, up to 168 days, plus loading doses)
Dosing Instructions:	Administer two SC injections of GSK3228836 for 300 mg dose, one SC injection of GSK3228836 for 150 mg dose (plus one SC placebo dose for blinding purposes)	Administer two SC injections for placebo
Manufacturer/Source of Procurement:	GSK GlaxoSmithKline Manufacturing SpA, Parma (Italy)	Locally sourced normal Saline
Method for Individualizing Dosage	Dispensing into syringes	Dispensing into syringes

SC=subcutaneous

The site of injection 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.

1. Abdominal quadrants
2. Thighs
3. Outer area of the upper arms
4. Buttocks

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 Study Reference Manual.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS 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.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding the participant on their intervention assignment is warranted. Participant

safety must always be the first consideration in making such a determination. If the investigator decides that unblinding to the participant is warranted, the investigator should make every effort to contact GSK prior to unblinding the participant to their intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK 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 case report form, as applicable.

Participants will be randomized in a 3:3:3:1 ratio to receive study intervention. Investigators will be unblinded to each participant's assigned study intervention throughout the course of the study.

Unblinded monitors and, in the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

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

GSK's Clinical Safety Department 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.

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.

6.5. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medications, including NAs (see Section 6.5.2 and Section 6.5.3), should be recorded.

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

6.5.1. Nucleos(t)ide Treatment during and after the End of the Study

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 (for participants on NA therapy at Baseline, participants are expected to continue their NA therapy over the duration of the study) and/or start standard of care treatment during the study period.

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.

For participants who are not receiving NA therapy at baseline, initiate NA therapy if ALT ≥3x ULN and bilirubin >1.5x ULN, as per Section 7.1.1 (Liver Chemistry Monitoring and Stopping Criteria). NA therapy may be subsequently discontinued if other tests (e.g., HBV DNA, HBsAg) rule out hepatitis B flare.

6.5.2. Initiation of Nucleos(t)Ides During GSK3228836 Treatment

The barrier to development of GSK3228836 resistance is unknown. Population sequencing of isolates from Study ISIS 505358-CS3 did not detect the development of mutations in the GSK3228836 binding site following 4 weeks of GSK3228836 monotherapy.

The risk of resistance development is expected to be lowest in participants receiving concomitant NA therapy due to the suppression of HBV viral replication. Ongoing viral replication during GSK3228836 treatment (e.g., due to virological breakthrough) may increase the risk of the development of resistance. Investigators should therefore consider initiation of NAs for participants not already receiving concomitant NA therapy and experience virological breakthrough whilst still receiving GSK3228836 (i.e., haven't completed treatment).

Virological breakthrough is defined as one of the following confirmed (2 sequential visits) lab results:

- ≥1 log increase from nadir of HBV DNA
- HBV DNA becoming quantifiable after being below the LLOQ

Initiation of NA therapy should also be considered for participants who are not receiving NA therapy at baseline, but are having either no response or only a partial response to GSK3228836 treatment (i.e. Treatment Arms 1 to 3, but not Arm 4 in participants not

currently on NA therapy). In Arm 4 of the participants not currently on NA therapy, NA will be withheld only during the initial 12-week placebo period. During the latter part of the study when the participants in Arm 4 are receiving active GSK3228836, NA therapy may be initiated as above if there is concern about developing resistance to GSK3228836.

No response to GSK3228836 treatment is defined as:

- By Week 12, <1 log decline in HBV DNA level from baseline

Partial response to GSK3228836 treatment is defined as:

- >1 log decline in HBV DNA, but subsequent plateau of HBV DNA levels such that achievement of HBV DNA below the LLOQ is considered unlikely

6.5.3. Initiation of Nucleos(t)ide Therapy Post GSK3228836 Treatment

Upon cessation of GSK3228836 treatment, participants, regardless of their baseline NA use or not, may experience virological relapse, DNA replication and an ALT flare. Investigators may, at their own discretion and in accordance with local guidelines, decide to initiate new or alternative NA therapy in these participants. Any treatment should be recorded as a concomitant medication.

6.5.4. 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 Screening through the final Follow-up visit (see Section 5.2; unless required for safety see Section 7)
- Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing
- Creatine-containing gym supplements
- Anti-coagulation therapies (e.g., warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel).

6.6. Dose Modification

Dose modifications are not planned for this study.

6.7. Intervention after the End of the Study

No intervention is planned at the end of the study, although participants may be asked to enrol in a long-term roll-over study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant may withdraw from the study treatment 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 administrative reasons. Participants that are discontinued from treatment will enter the post-treatment period unless consent is withdrawn. Every effort should be made to complete the early termination (ET) study procedures and observations if the participant does not enter post-treatment follow-up.

Any laboratory parameter that meets the stopping criteria should be repeated to confirm the value prior to withdrawal

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant may remain in the study to be evaluated for safety and efficacy assessments. For participants meeting the stopping criteria (Section 7.1.1-Section 7.1.4), participants should be monitored until laboratory abnormalities resolve, stabilize, or return to within baseline values as indicated. The participant must then attend the follow-up visits specified in the SoA. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Monitoring and Stopping Criteria

Liver chemistry monitoring and stopping criteria have been designed to assure participant safety and to evaluate liver event etiology. Study intervention will be discontinued for a participant if the liver stopping criteria are met. Restart/re-challenge guidelines are presented in Section 10.6.

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

- a participant meets one of the discontinuation conditions outlined in Table 6
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Table 6 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. The participant must then attend the follow-up visits specified in the SoA.

Every attempt must be made to have the participant evaluated (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. Upon completion of the safety follow-up procedures (see below), the participant must attend the follow-up visits specified in the SoA.

Table 6 Liver Chemistry Monitoring and Stopping Criteria-

ALT Level	Monitoring Plan	Discontinuation
10x ULN ≤ ALT <12x ULN **and** Bilirubin ≤1.5x ULN **and** INR ≤1.5 (if available)	Monitor twice weekly Additional lab assessments	Permanently discontinue IMP if ALT >10x ULN >4 weeks
ALT ≥12x ULN **and** Bilirubin≤1.5x ULN **and** INR ≤1.5 (if available)	Hold dose Monitor twice weekly Additional lab assessments if not already done Take off hold: 150 mg SC weekly when ALT <10x ULN; increasing dose to 300 mg (if applicable) should be agreed with Medical Monitor	Permanently discontinue IMP if any of the following apply: • ALT ≥10x ULN >4 weeks • ALT ≥12x ULN recurs after IMP taken off hold
ALT ≥3x ULN **and** 1.5x ULN <bilirubin ≤2x ULN (>35% direct) **and** INR ≤1.5 (if available)	Hold dose Monitor twice weekly Additional lab assessments if not already done Take off hold: 150 mg SC weekly when bilirubin returns to <1.5x ULN; increasing dose to 300 mg (if applicable) should be agreed with Medical Monitor *For participants not receiving NA therapy at baseline, initiate NA therapy*[1]	Permanently discontinue IMP if the following recurs after IMP taken off hold: 1.5x ULN <bilirubin ≤2x ULN (>35% direct) **And** INR ≤1.5 (if available)
ALT ≥3x ULN **and** any of the following apply: • bilirubin >2x ULN (>35% direct) • associated with the appearance or worsening of hepatitis symptoms • INR >1.5 (if available)		Permanently discontinue IMP Monitor twice weekly until stable ALT Additional lab assessments if not already done *For participants not receiving NA therapy at*

ALT Level	Monitoring Plan	Discontinuation
		baseline, initiate NA therapy[1]

ALT = alanine aminotransferase; IMP = investigational medicinal product; ULN = upper limit of normal
1. NA therapy may be subsequently discontinued if other tests (e.g., HBV DNA, HBsAg) rule out hepatitis B flare.

*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 in the liver parameters must be confirmed by retesting ALT, total bilirubin, direct bilirubin, and INR (if available).
- If one criterion in the list above is met and confirmed by retesting, further treatment may be discontinued for this participant after discussion with the Medical Monitor. 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 6:

- 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 pharmacokinetic (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 Study Reference Manual (SRM).

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

Review fractionated bilirubin

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 Adverse Event (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 Alcohol 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]), if available.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) or Liver biopsy to evaluate liver disease.

- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

7.1.2. Drug Induced Vascular Injury and Complement Stopping Criteria

If any of the following are observed, results should be confirmed with a repeat sample collection and analysis**,** and if confirmed, further evaluation for alternative causes should be pursued in consultation with the Medical Monitor.

Repeat sample collection of C3, C4, Bb, C5a would be triggered by changes in the clinical signs and symptoms of complement activation (≥2+ haematuria; increasing urine ACR; vasculitic or purpuric rash; peripheral neuropathy; jaundice). Additional complement analyses for example CH50, Factor B level, Factor H level, sC5b-9 should also be considered in discussion with the Medical Monitor and Safety Panels.

1. **Persisting & deteriorating longitudinal trends in change from baseline for C3 and/or C4 defined as:**
   a. If participant's baseline C3 and/or C4 is ***within*** the lab's normal range at baseline: there is a sequential decline in C3 and/or C4 once levels have fallen below LLN for ≥4 weeks OR
   b. If participant's baseline C3 and/or C4 is ***below*** the lab's LLN at baseline: there is further sequential decline in C3 and/or C4 for ≥4 weeks OR
   c. Regardless of baseline C3 and/or C4 level: there is a ***≥80% reduction*** in the participant's C3 and/or C4 level at any point

   AND

   d. There is an associated ***≥3-fold increase*** in Bb and/or C5a from participant's baseline OR
   e. There are associated biochemical sequelae for example, a rising high sensitivity C-reactive protein (hs-CRP); rising monocyte chemoattractant protein-1 (MCP-1); new thrombocytopenia, new renal impairment with no other explanation such as intercurrent infection OR
   f. There are associated clinical sequelae, for example, ≥2+ haematuria; increasing urine ACR; vasculitic or purpuric rash; peripheral neuropathy; jaundice OR
   g. There is new cANCA or pANCA positivity

2. **Persisting & deteriorating longitudinal trends in change from baseline for Bb and/or C5a where**
   a. There is a ≥3-fold increase in Bb and/or C5a over baseline

   AND

   b. This is persisting or increasing week on week in sequential data plots OR
   c. There are associated biochemical sequelae for example, a rising hsCRP; rising MCP-1, new thrombocytopenia, new renal impairment with no other explanation such as intercurrent infection OR
   d. There are associated clinical sequelae, for example, ≥2+ haematuria; increasing urine ACR, vasculitic or purpuric rash; peripheral neuropathy; jaundice or any combination of these OR
   e. There is new cANCA or pANCA positivity

Treatment Hold/Treatment Discontinuation

- Hold study treatment during evaluation of alternative causes for decreased C3 and/or C4 associated with increased inflammatory markers including one or more of hs-CRP, MCP-1, Bb and C5a
- Discontinue study treatment permanently if persistent change from baseline (≥4 weeks) in biomarker pattern (decreased C3/C4 associated with increased inflammatory markers including one or more of hsCRP, MCP-1, Bb, C5a) without clear alternative explanation.
- Discontinue study treatment permanently if suspect clinical sequelae of complement activation, drug induced vascular injury, vasculitis or auto-immunity regardless of biomarkers changes or persistence.

7.1.3. Haematological Stopping Criteria

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 a decreasing trend is noted below LLN reference range, re-check the platelet counts as soon as possible (the investigator may, at their discretion, opt to have the participant come to their next scheduled visit OR ask the participant to come earlier than their scheduled visit, as they feel appropriate based on review of the participant's clinical presentation and laboratory results). Samples showing platelet clumping should also be repeated.

Participants with platelet values below 75 x 10^9/L 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 permanently. Monitor until platelet abnormalities resolve, stabilize, or return to within baseline values.

Table 7 Haematological Stopping Criteria

Platelet Count	Monitoring	Treatment
75 X 10^9/L ≤ Platelets <100 X 10^9/L	Monitor weekly, results of local platelet count must be available prior to dosing	Hold treatment until platelets return to ≥100 x10^9/L [if positive for anti-platelet antibodies, study treatment should be discontinued immediately]
50 X 10^9/L ≤ Platelets1 <75 X 10^9/L	Monitor every 2-3 days until three successive measurements ≥75 x10^9/L, then weekly Assess anti-platelet antibodies	
<50 x 10^9/L	Monitor daily until ≥25 x10^9/L, monitor every 2-3 days until three successive measurements ≥75 x10^9/L, then weekly until platelets ≥100 x10^9/L Assess anti-platelet antibodies	Discontinue treatment permanently Glucocorticoids recommended (unless the participant has a medical contraindication to receiving glucocorticoids), and discontinuation of any antiplatelet medicinal products/NSAIDs/anticoagulants

7.1.4. Drug Induced Kidney Injury (Renal) Stopping Criteria

If any of the following are observed, results should be confirmed**,** and if confirmed, further evaluation for alternative causes should be pursued in consultation with the Medical Monitor:

- Persistent ACR ≥0.03 mg/mg (≥30 mg/g)
- Blood in urinalysis ≥5 RBC per high power field (HPF) confirmed by urine microscopy

- Persistent elevation of serum creatinine (>26.52 μmol/L or 0.3 mg/dL change from baseline)

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

Treatment Hold/Treatment Discontinuation

- Hold study treatment in participants who develop ACR ≥0.5 mg/mg (500 mg/g), or eGFR >25% reduction from pre-dose range, pending consultation with the Medical Monitor and further evaluation of the cause.
    - If a dose is held, once eGFR increases to within baseline, ACR decreases to <0.5 mg/mg (500 mg/g), or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated after consultation with the Medical Monitor
    - Participants must be monitored weekly until ACR or eGFR resolve, stabilize, or return to within pre-dose range
- Hold study treatment in participants with ACR ≥2 mg/mg (2000 mg/g), perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed or probable (i.e., meets clinical definition of rapidly progressive glomerulonephritis [RPGN] if biopsy not feasible), GSK3228836 should be permanently discontinued
    - Participants must be monitored weekly until ACR resolves, stabilizes, or returns to within baseline values
- Delay in treatment of suspected RPGN should be avoided.

7.1.5. Study Intervention Restart or Rechallenge after stopping criteria met

Study intervention rechallenge after stopping criteria are met (i.e., study treatment discontinued) by any participant in this study is not allowed. Study intervention restart may be considered only for liver events as follows:

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Intervention

Restart refers to resuming study intervention following liver stopping events in which there is a clear underlying cause (other than drug-induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis).

Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

- Approval by GSK for study intervention restart can be considered where:
  - Investigator requests consideration for study intervention restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
  - Possible study intervention-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study intervention has a confirmed genetic marker associated with liver injury, the presence of the marker should be excluded. If study intervention-related liver injury cannot be excluded, the guidance on rechallenge will apply.
  - There is no evidence of alcohol-related hepatitis.
  - Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approval of study intervention restart has been obtained (if required).

If restart of study intervention is approved by GSK Medical Governance in writing:

- the participant must be provided with a clear description of the possible benefits and risks of study intervention administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart of study intervention (refer to Section 10.1.3). Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by GSK
- Participants approved by GSK for restart of study intervention must return to the clinic twice a week for liver function tests until stable liver function tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the participant meets protocol-defined liver chemistry stopping criteria after study intervention restart, study intervention should be permanently discontinued.
- The Medical Monitor, and the IRB/IEC, must be informed of the outcome for the participant following study intervention restart.
- GSK must be notified of any adverse events.

For treatment that has been placed on hold, please follow the guidelines above (Section 7.1.1 to Section 7.1.4).

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, behavioral, compliance or administrative reasons.

- The investigator may ask participants to withdraw from study treatment, but continue with post-treatment follow up visits instead of withdrawing completely from the study.
- At the time of discontinuing from the study, if possible, an early termination 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.

7.3. 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 Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- In selected sites/countries, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments

and data collection. The full specifications of the home nursing services will be outlined in the SRM

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

8.1. Efficacy Assessments

The primary objective measurements for efficacy include:

- HBsAg
- HBV DNA

HBsAg and HBV DNA are collected as per the SoA. Details of sample collection can be found in the SRM.

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 GSK3228836 treatment which is sustained for 24 weeks post-GSK3228836 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 24 weeks from end of GSK3228836 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. Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.2.1. Physical Examinations

A complete physical exam will be conducted at the Screening visit. Symptom-directed exams will be conducted at all other time points.

- A complete physical exam will include, at a minimum, assessment of the dermatologic, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded (with participant wearing daytime clothing with no shoes).
- A symptom-directed exam will include, at a minimum, assessments of the dermatologic, cardiovascular, respiratory, and gastrointestinal systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Injection Site Reactions

Injection Site Reactions (ISRs) are any experiences which occur at the site of injection of the study treatment. Participants will be monitored closely for ISRs and ISRs should be recorded as AEs

Injection site reactions will be graded according to the criteria provided in the Division of AIDS (DAIDS) grading table (see Appendix 3).

8.2.3. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed 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).
- Vital signs will be measured in a semi-supine position (preferred, but not required) after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- If assessments are scheduled for the same nominal time, then 12-lead ECG and vital signs must be completed prior to blood collection. The order of conducting the 12-lead ECG and vital sign measurements is flexible but should allow the blood collection to occur at the exact nominal time.

8.2.4. Electrocardiograms

The ECG is for screening purposes only.

Single 12-lead ECG will be obtained locally 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. Manual calculation, if an automatic calculation is not available, is acceptable.

8.2.5. Clinical Safety Laboratory Assessments

Refer to 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 relevant changes occurring during the study in the AE Section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- If such values do not return to normal/baseline or are still considered significantly abnormal by the investigator by the participant’s last visit, additional follow-up should be discussed with the sponsor.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 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).

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

- All AEs and SAEs will be collected from the signing of the informed consent until the final follow-up visit at the time points specified in the SoA (Section 1.3). However, AEs and SAEs that occur prior to the first administration of investigational medicinal product should be recorded only if assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek 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

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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 all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a 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.

8.3.5. Pregnancy

- Details of all pregnancies in female will be collected after the start of study intervention and until no longer than 6 to 8 weeks following the estimated delivery date.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events 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

8.3.7.1. 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 7.1.1

8.3.7.2. Vascular Inflammation and Complement Activation

Inflammatory and immune changes are recognized as a class effect of ASOs. Despite the low risk for ASO-related vascular adverse events in patients, the nature of the toxicity demands a conservative approach to care and monitoring to ensure the safety of participants. Because the complement-mediated mechanism of vascular inflammation in monkeys has been well established, a monitoring strategy has been proposed in participants that encompasses a multi-pronged approach for monitoring of this toxicity, from separate mechanistic, phenotypic and organ-specific perspectives.

Vascular inflammation will be monitored through various inflammatory markers (e.g., complement factors, hs-CRP, ANCA, MCP-1) and presence of clinical signs and symptoms.

A monitoring strategy of vasculitis and complement activation is presented in Section 7.1.2

8.3.7.3. 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 7.1.3

8.3.7.4. 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, ACR) is presented in Section 7.1.4

8.3.7.5. Injection Site Reactions

Injection site reactions were the most commonly reported treatment-related adverse event in previous studies with GSK3228836. 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.

8.4. Treatment of Overdose

For this study, any dose of GSK3228836 greater than 300 mg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3228836 can no longer be detected systemically (at least 105 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
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 in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of GSK3228836 and/or nucleos(t)ide as specified in the SoA.

- For standard PK sampling, one pre-dose PK sample at each visit during the treatment period (except for Day 4 and Day 11) and one PK sample at any time at each visit during the off-treatment period will be collected in participants from all 8 study arms.
- For intensive PK sampling, a maximum of 13 samples in addition to the standard PK sampling may be collected from 39 participants who were on stable NA therapy at baseline (13 in each region of Japan, China, and non-Asian country/ies) at one additional time point during the study. The intensive PK sampling will be collected at one visit between Week 14 (inclusive) and Week 24 (inclusive), chosen between the site and participant. See Table 8 for sample collection timings. 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.

- At the visit for intensive PK sampling, GSK3228836 and nucleos(t)ide will be administered as close together as possible, and the date and time (24-hour clock time) of administration of both drugs will be recorded. Instructions for drug administration at the visit for intensive PK sampling will be provided by the sponsor. See SRM for details.
- 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.
- Standard PK samples will be used to evaluate the PK of GSK3228836, and explore PK-PD relationships.
- For participants in the intensive PK sampling, samples will be used to evaluate the PK of GSK3228836 and nucleos(t)ide therapy. See Table 8.
- Samples collected for PK analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which plasma samples for the determination of multiple aspects of GSK3228836 will be taken, one sample of sufficient volume can be used.
- Drug concentration information and accompanied CRF information that would unblind the study will not be reported to blinded GSK personnel until the study has been unblinded. See SRM for details.

Table 8 Sample Collection Schedule for Intensive PK Sampling

	Pre-Dose	0.5 hr	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr	8 hr	12 hr	24 hr	72 hr	168 hr[1]
GSK3228836	X		X		X	X	X	X	X	X	X	X	X	X
Nucleos(t)ide	X	X	X	X	X	X	X	X	X	X	X	X		

1. The 168 hr timepoint occurs approx. 7 days (±24 hrs) after the dose. The site should align this PK timepoint collection with the next study visit as close to the nominal timepoint as possible (±24 hrs), then the 168 hr PK can be collected as the next pre-dose PK sample (for example if the participant has their intensive PK visit at Week 16 then the pre-dose PK at Week 17 would suffice and a separate 168 hr PK collection is not required, decreasing the participant's scheduling burden)

8.6. Pharmacodynamics

Pharmacodynamic parameters explored in this study will include but are not limited to:

- Categorical: virologic response, seroclearance (HBsAg), HBV DNA level below LLOQ, and seroconversion (HBsAb and HBeAb);

- Change from baseline: HBsAg, HBV DNA, HBeAg, and HBsAb levels.

- Time to event: virologic response, nadir of HBsAg and HBV DNA, seroclearance (HBsAg), HBV DNA level below LLOQ, seroconversion (HBsAb and HBeAb); peak of ALT flares;

- Safety assessments including but not limited to vital signs, electrocardiograms, laboratory measurements and adverse events.

8.7. 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.

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 Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

8.8. Biomarkers

Collection of samples for other biomarker research is also part of this study. These exploratory biomarker samples will be collected to evaluate the pathogenesis of CHB; the absorption, distribution, metabolism, or excretion of GSK3228836; or the participant's response to GSK3228836. In addition, continuing research may identify other proteins, transcripts or biomarkers related to GSK3228836 treatment, the response to GSK3228836 or the pathogenesis of CHB, which will be evaluated in these samples.

- Blood samples, including serum, plasma, PBMCs and PAXgene tubes, will be collected to evaluate virologic and immune biomarkers related to the pathogenesis of CHB and the participant's response to GSK3228836. Samples will be collected according to the schedule described in the SoA and as detailed in the laboratory manual provided separately to sites.

- GSK may store samples for up to 15 years after the end of the study. The archived samples may be used 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.). The archive samples may also be used for studying biomarkers that may be affected by treatment, such as HBcrAg, HBV RNA or indoleamine 2,3 dioxygenase (IDO), or other immune-related responses. Additionally, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of chronic hepatitis B or other diseases, the development of related or new treatments or research methods.

For China, see Appendix 7 on biomarkers.

8.9. HBV Resistance Monitoring

Samples collected for viral genotyping and phenotyping may be used for HBV resistance mutation analysis. Viral DNA and/or viral RNA will be extracted from participant samples and the viral genome will be DNA sequenced to determine whether mutations have occurred in the GSK3228836 binding region or elsewhere in the genome (and if applicable, whether any known nucleos(t)ide resistance mutations are present in the polymerase coding region).

Resistance monitoring will be conducted on all baseline isolates to identify pre-existing substitutions. Sequencing of the viral RNA will be attempted in participants receiving stable NA therapy and having DNA <LLOQ. Additional resistance monitoring will be conducted and will include, but not limited to, the analysis of isolates from participants experiencing virological failure during or post treatment as defined below. Confirmation of resistance should be done within 1 week after results are received.

8.9.1. Resistance Analysis based upon HBV DNA Criteria

HBV DNA for each participant will be measured throughout the study. HBV resistance monitoring will include analysis of isolates from participants experiencing virological failure.

Virologic failure is defined as the following confirmed (2 sequential) lab results;

- ≥1 log increase from nadir of HBV DNA OR
- HBV DNA becoming quantifiable after being below the LLOQ OR
- Never achieved HBV DNA levels less than LLOQ

8.9.2. Resistance Analysis based upon HBsAg Criteria

HBsAg levels for each participant will be measured throughout the study. In addition to the standard HBV DNA virological failure criteria defined above, HBV resistance monitoring will also include analysis of isolates from participants experiencing HBsAg seroreversion in the absence of detectable HBV DNA.

HBsAg seroreversion is defined as the following confirmed (2 sequential) lab results;

- ≥1 log increase from nadir of HBV HBsAg OR
- HBV HBsAg becoming quantifiable after being below the LLOQ OR
- Never achieved HBsAg levels less than LLOQ

8.10. Patient Reported Outcomes (PROs)

8.10.1. Hepatitis B Quality of Life (HBQOL)

The HBQOL has been designed to assess quality of life in patients with Hepatitis B. It consists of 31 items and 6 domains: psychological well-being, anticipation anxiety, vitality, stigma, transmissibility and vulnerability. Response options range from 1 to 5 with higher scores indicating more severe impact of Hepatitis B than lower scores.

8.10.2. EQ-5D-3L

The EuroQOL (EQ-5D-3L) is a standardized instrument for use as a measure of health status that is applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status that can be used in evaluation of health care. The EQ-5D-3L is designed for self-completion by patients, and is cognitively undemanding, taking only a few minutes to complete. Instructions to participants are included in the questionnaire.

The EQ-5D-3L consists of 2 parts: the EQ-5D descriptive items and the EQ visual analog scale (EQ VAS). The EQ-5D comprises 5 dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is ranked on 3 levels. The participant is asked to indicate his/her health state by ticking in the box against the most appropriate statement for each of the 5 dimensions.

The EQ VAS records the participant's self-rated health on a vertical VAS with endpoints labelled "the best health you can imagine" and "the worst health you can imagine". The instructions ask the participant to mark an X on the scale to indicate how your health is TODAY and then to write the number marked on the scale in the box below the scale.

8.11. Survey Questionnaires

Patient App

Participants will be provided the option of downloading a patient app on their cellphone at the start of the study, which will be used primarily to assist in visit tracking and providing general information about the study.

This app will contain an optional survey that participants can complete and will ask questions about their experience participating in the study. No formal analysis will be conducted on this data. This data will be used to drive patient focus in future studies with GSK3228836.

Patient Feedback on Dosing Regiment

Participants will be asked questions about their experience of the dosing regimen used in the study. This data may be used to drive patient focus in future studies with GSK3228836.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of the study is to assess the efficacy of three dosing regimens (arms 1, 2, and 3) of GSK3228836 in participants with CHB as described in Section 4.1. Note that loading vs. no loading dose (arm 3 vs. arm 4) is assessed in an exploratory objective. The primary endpoint is achieving a sustained virologic response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. Rescue medication is defined as any medication initiated for the purpose of antiviral suppression.

An estimation approach with no hypothesis testing will be used to address the primary objective. The primary assessments of interest are the point estimate of SVR rate and 95% credible intervals; in addition, posterior probabilities that the true SVR in each treatment arm is greater than a range of clinically meaningful response rates will be provided. The point estimates for SVR will be calculated using a Bayesian probability approach. Comparisons between treatment arms as defined in the key secondary/exploratory objectives will be assessed using probability inference approaches.

9.2. Sample Size Determination

Approximately 440 participants are planned to be randomly assigned to study intervention.

For each population, there will be approximately 66 participants assigned in each of the first three arms. There will be approximately 22 participants assigned in the fourth arm.

It is assumed that the number of responders follows a Binomial distribution, with a weakly informative prior (Beta (0.5, 0.5)) for the true response rate. The precision for a range of response rates with 95% credible intervals are shown in Table 9.

Table 9 95% Credible Interval of Response Rate by Sample Size

Sample size per arm	Number of responders	Response rate	95% credible interval*
22	2	9%	1% – 23%
	3	14%	3% - 30%
	4	18%	5% - 36%
	5	23%	8% - 41%
	6	27%	11% - 46%
66	6	9%	3% - 17%
	9	14%	6% - 23%
	12	18%	10% - 28%
	15	23%	13% - 33%
	18	27%	17% - 38%

*95% highest posterior density interval

The lower bounds of 95% credible intervals will exclude the historical placebo response rate of 3% if observed response rate is greater than or equal to 14% in arms 1-3 or 18% in arm 4.

The posterior probabilities that the true sustained virologic response rate is greater than a range of response rates will be calculated from the implied Beta posterior, given the actual number of responders observed.

The operating characteristics based on at least 75% posterior confidence that the true rate exceeds a threshold of interest, are shown in Table 10, for various sample sizes, and true cure rates. The operating characteristics shown are based on a Bayesian model without consideration of baseline stratification factors and expected to be similar to operating characteristics from the hierarchical model defined in Section 9.4.3.

Table 10 End of Study Operating Characteristics by Sample Size

Criterion	**Sample size per arm**	**Minimum number (%) of responders required to meet Criterion**	**Probability of Meeting Criterion Under Various Assumptions**			
			True Resp Rate=5%	**True Resp Rate=20%**	**True Resp Rate=25%**	**True Resp Rate=30%**
Probability (true response rate>15%)>75%	22	5 (23%)	0%	46%	68%	84%
	44	9 (20%)	0%	53%	81%	91%
	66	**12 (18%)**	**0%**	**69%**	**93%**	**99%**
	88	16 (18%)	0%	71%	95%	100%
Probability (true response rate>20%)>75%	22	6 (27%)	0%	27%	48%	69%
	44	11 (25%)	0%	25%	56%	81%
	66	**16 (24%)**	**0%**	**23%**	**60%**	**88%**
	88	21 (24%)	0%	22%	64%	92%
Probability (true response rate>25%)>75%	22	7 (32%)	0%	13%	30%	51%
	44	13 (30%)	0%	9%	29%	58%
	66	**19 (29%)**	**0%**	**6%**	**28%**	**63%**
	88	25 (28%)	0%	4%	27%	67%

Note: If the true response rate is 0%, the probability of meeting each criterion is 0% for all sample sizes.

Based on these operating characteristics, for a true response rate of 20%, the proposed sample-size of n=66 for arms 1 – 3 has ~70% probability of confirming a true response of at least 15%, and if the true rate is 30%, there is an 88% chance of confirming a true response of at least 20%.

There are no plans for sample size re-estimation.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility
Enrolled	• All participants who passed screening and entered the study • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study
Intent-to-Treat (ITT)	• All randomized participants. • This population will be based on the treatment the participant was randomized to • Any participant who receives a treatment randomization number will be considered to have been randomized
Safety	• All participants who were randomized and received at least one dose of study treatment • This population will be based on the treatment the participant received. • Note: Participants who were not randomized but received at least one dose of study treatment will be listed
Pharmacokinetic (PK)	• 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) • Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded
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 will be finalized prior to unblinding 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. All summaries and analyses will be conducted separately for the 2 populations (on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment). No adjustments will be made for multiplicity.

9.4.1. General Considerations

Unless otherwise specified, baseline will be the last value/assessment before the first dose of study treatment (Day1 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)

Analyses will be conducted separately for the on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment populations. The primary analysis for the primary

endpoint will be conducted once the last participant has completed the Week 48 visit and database lock has been achieved.

The primary efficacy endpoint is achieving a sustained virologic response for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. Sustained virologic response is defined as observing HBsAg <LLOQ and HBV DNA <LLOQ at each analysis window in the 24 weeks after the end of GSK3228836 treatment. Analysis windows for the post GSK3228836 treatment assessments will be defined in the analysis plan.

HBsAg and HBV DNA from Week 24 to Off-Treatment Week 24 will be used to assess the primary endpoint for arms 1 and 2, and the exploratory endpoint for arm 4. For dosing schedule of arms 1, 2, and 4, see Section 4.1.

For arm 3, because of the shortened time on treatment (12 weeks instead of 24 weeks), post-treatment visit schedules will not match those of arms 1 and 2. To avoid risk of bias the following visits have been selected for arm 3 to match the number and timing of visit windows for measuring off-treatment virologic responses in arms 1 and 2 to evaluate the primary endpoint

- Week 12, 13, 14, 16, 20, 24, off-treatment Week 4, 8, 12

9.4.2.1. Primary Estimands

Primary Estimands supporting the primary objective are defined as:
- **Population**: separate assessment for the following:
  - participants with CHB on stable nucleos(t)ide therapy
  - participants with CHB not currently on nucleos(t)ide therapy
- **Variable**: Sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication.
- **Treatments**: arms 1, 2, and 3. Estimation of the within-arm response rate. Note: arm 4 is described in Section 9.4.2.2
- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).

- **Population summary**: proportion of participants who achieve SVR for each treatment arm.

The primary estimands for each sub-population is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.

9.4.2.2. Supplementary Estimands

A supplementary estimand is defined to support the primary objective. The supplementary estimand is defined in the same way as the main estimand, except the assessment time frame for participants achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the actual end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

9.4.2.3. Handling of Withdrawal from Study and Missing HBsAg and HBV DNA Data

Two approaches will be used to determine a participant's response when HBsAg and HBV DNA data are missing from visits required to derive the primary endpoint.

1) For participants where wide disruptive events (such as COVID-19 pandemic) prevent assessment of the primary outcome, SVR will be imputed using all available data for participants for whom SVR can be assessed. For other participants where SVR in the absence of rescue medication cannot be ascertained due to missing data (withdrawal from the study or missing due to other reasons, but not due to a wide disruptive event), the participant will be assumed not to have achieved SVR (non-responder imputation).

2) For the primary estimands, a sensitivity analysis will be performed using the Bayesian model described in Section 9.4.3 assuming missing at random whereby a participant's response will be imputed using all available data (on and off treatment values) for participants who completed the study.

9.4.3. Primary Analyses

All analyses will be conducted separately for the 2 populations (on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment). The participant population will not be included as a stratification factor in the analysis model.

The primary assessments of interest are the point estimate of sustained virologic response rate and 95% credible intervals; in addition, posterior probabilities that the true virologic response rate in each treatment arm is greater than a range of values will be provided.

A Bayesian hierarchical model will be used to estimate the posterior probability of sustained virologic response rate for each arm incorporating the baseline stratification factors [Jones, 2011].

Model for each arm:

$$Number\ of\ responders\ r_g \sim Binomial(n_g, p_g), \qquad g = 1,2,3,4$$

$$\theta_g = \text{logit}(p_g) = \log\left(\frac{p_g}{1-p_g}\right) = \gamma_0 + \gamma_1 I_{\{B1+\}} + \gamma_2 I_{\{B2+\}} + \psi_g,\ g = 1,2,3,4$$

where $\gamma_0, \gamma_1, \gamma_2, \psi_g$ are all parameters. Thus,

$$\theta_1 = \gamma_0 + \psi_1$$

$$\theta_2 = \gamma_0 + \gamma_1 + \psi_2$$

$$\theta_3 = \gamma_0 + \gamma_2 + \psi_3$$

$$\theta_4 = \gamma_0 + \gamma_1 + \gamma_2 + \psi_4$$

Priors:

$$\gamma_k \sim Normal\left(0, 10^6\right), k = 0,1,2$$

$$\psi_g \sim Normal(0, \omega^2), g = 1,2,3,4$$

$$\omega \sim Half - normal(1)$$

Where we define r_g as the number of SVR responders among n_g participants, p_g as SVR rate, θ_g as the log odds of treatment response $\log(\frac{p_g}{1-p_g})$, index g =1,...,4 refers to the stratum number, γ_k represent fixed effects of baseline stratification factors (see below), and ψ_g denotes a random effect in stratum g.

The four strata and representation of the two baseline stratification factors B_1 and B_2 in the model are shown in Table 11.

Table 11 Baseline Stratification Factors for Four Stratum

Stratum	B_1: HBsAg ($I_{\{B1+\}}$)	B_2: HBeAg ($I_{\{B2+\}}$)
1: HBsAg ≤3 log IU/mL and Negative HBeAg	B_{1-} (≤3 log IU/mL) (0)	B_{2-} (Negative) (0)
2: HBsAg >3 log IU/mL and Negative HBeAg	B_{1+} (>3 log IU/mL) (1)	B_{2-} (Negative) (0)
3: HBsAg ≤3 log IU/mL and Positive HBeAg	B_{1-} (≤3 log IU/mL) (0)	B_{2+} (Positive) (1)
4: HBsAg >3 log IU/mL and Positive HBeAg	B_{1+} >3 log IU/mL) (1)	B_{2+} (Positive) (1)

For each arm, the posterior distribution of SVR rate P(p_g|data), g=1,2,3,4 will be derived for each stratum using the model specified above.

The posterior distribution of the arm-level SVR rate will be derived using a mixture of the posterior distributions of SVR rate for each stratum in that arm. The weights are proportional to the sample size of each stratum.

Posterior probability of sustained virologic response rate exceeding a range of clinically meaningful response rates will be generated using the approach specified above for each arm.

9.4.4. Secondary Endpoint(s)

9.4.4.1. Estimands for Secondary Objectives:

All analyses will be conducted separately for the 2 populations (on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment).

Two groups of estimands are defined for the secondary efficacy objectives.

Categorical definitions for secondary analyses will be provided in the RAP.

Estimands supporting secondary objective of assessing the efficacy of GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows:

- Population: one subpopulation of participants with CHB on stable nucleos(t)ide therapy and a second subpopulation of participants with CHB not currently on nucleos(t)ide therapy.
- Treatments: arms 1-4. Estimation within each arm.
- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication will be ignored (treatment policy strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy)

1) Categorical Variables:

- Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment.
- Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 $\log_{10}$ IU/mL) and in HBV DNA (e.g. <1, ≥1, ≥2, ≥3 log IU/mL). Additional categories of changes from baseline may be added in the RAP.
    - ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN

    - HBe antibody (anti-HBeAg) levels

- **Population summary:** proportion of participants in each category for each treatment arm.

2) Continuous Variables: Actual values and change from baseline over time of HBsAg and HBV DNA and actual values and change from baseline of HBeAg levels; HBs antibody (anti-HBsAg) levels.

- **Population summary**: mean values and mean changes from baseline for each variable in each treatment arm

3) Time to Event Variable: Time to ALT normalization in absence of rescue medication in participants with baseline ALT>ULN

- **Population summary**: Turnbull's estimator for non-parametric estimation of Time to ALT normalization in each treatment arm

The group of estimands supporting this objective for each sub-population are the population summary for each variable in each treatment arm 1-4 regardless of completing IP, interruptions in IP or adherence to IP and regardless of rescue medication (except for ALT normalization which can only be achieved in the absence of rescue medication).

Missing data for variables defined above (except for Time to ALT normalization) will be ignored, only available data will be summarized. For participants who withdraw from the study or Participants with ALT>ULN at the end of study, time to ALT normalization will be censored at the time of last visit. No sensitivity analysis is planned for the group of estimands supporting this objective. Further details will be provided in the RAP.

- Estimands supporting secondary objective of comparing the efficacy between 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of GSK3228836 treatment are defined as follows:
  - **Population**: separate assessment for the following:
    - participants with CHB on stable nucleos(t)ide therapy
    - participants with CHB not currently on nucleos(t)ide therapy
  - **Variable**: Sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication.
  - **Treatments**: arms 1, 2, and 3. Three treatment comparisons between: arms 1 and 2, arms 1 and 3, and arms 2 and 3.
  - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).
  - **Population summary**: difference in proportion of participants who achieve SVR between treatment arms.

The group of estimands supporting this objective for each sub-population are the difference in each treatment comparisons in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.

The non-responder imputation described in Section 9.4.2.2 will be used when HBsAg and HBV DNA data are missing from visits required to derive the endpoint. Further details will be provided in the RAP.

9.4.4.2. Secondary Efficacy Analyses

Secondary efficacy comparisons of interest include difference in sustained virologic response rate between following treatment arms:

- Arm 1 vs. Arm 2
- Arm 1 vs. Arm 3
- Arm 2 vs. Arm 3

Comparisons between the treatment arms will be conducted using a similar model specified in Section 9.4.3 but defining θ_g as the log odds ratio of treatment effect comparing one treatment arm to another treatment arm. The point estimates of differences in sustained virologic response rate with 95% credible intervals will be calculated for the treatment comparisons described in the estimands. Details of the model are included in the RAP.

9.4.4.3. Historical placebo:

Summary-level historical placebo data over 48 weeks from publications may be included in a supplementary analysis. A longitudinal model including historical response at 12, 24 and 48 weeks of placebo treatment will be constructed. For the first 12-week period, the model will allow dynamic borrowing from historical placebo data to the concurrent placebo in Weeks 1-12 in arm 4. Furthermore, the model will provide longitudinal prediction of response at Week 24 and Week 48 for participants in arm 4 (had they continued on Placebo rather than switching to GSK3228836 treatment). Descriptive comparisons will be included in summary tables and figures as appropriate. Further details will be provided in the RAP.

9.4.5. Safety Endpoints

Safety analyses

All analyses will be conducted separately for the 2 populations (on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment).

All safety analyses will be based on the Safety Population.

Exposure to study medication, measured by the number of injections and proportion of planned number of injections of study drug, will be summarized by treatment arm.

The proportion of participants reporting adverse events (AEs) will be tabulated for each treatment arm. The following summaries of AEs will be provided:

- Incidence and severity of All AEs;
- Incidence and severity of treatment related AEs;
- Incidence and severity of AEs leading to withdrawal from study;
- Incidence of serious AEs (SAEs).

Laboratory data, vital signs and ECG data (absolute values and change from Baseline) will be summarized by visit and treatment group. In addition, the maximum post-baseline toxicity grade (based on DAIDS categories) will be tabulated by treatment arm.

Details of exploratory analyses for exploratory efficacy, virology, and biomarker will be provided in the RAP. The results of HBcrAg, HBV RNA, virology and biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9.4.6. Exploratory Objectives

9.4.6.1. Estimand for Exploratory Objectives

- Estimands supporting exploratory objective of comparing the efficacy between 12 weeks of GSK3228836 treatment with a loading dose or without a loading dose are defined as follows:
  - **Population**: separate assessment for the following:
    - participants with CHB on stable nucleos(t)ide therapy
    - participants with CHB not currently on nucleos(t)ide therapy
  - **Variable**: Sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication.
  - **Treatments**: arm 3 and 4. Treatment comparison between arms 3 and 4.
  - **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).
  - **Population summary**: difference in proportion of participants who achieve SVR between treatment arms 3 and 4.

The group of estimands supporting this objective for each sub-population are the differences between arms 3 and 4 in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.

The non-responder imputation described in Section 9.4.2.2will be used when HBsAg and HBV DNA data are missing from visits required to derive the endpoint. Further details will be provided in the RAP.

Comparisons between the treatment arms 3 and 4 will be conducted using the same model specified in Section 9.4.2.2 but defining θ_g as the log odds ratio of treatment effect comparing one treatment arm to another treatment arm, further details will be included in the RAP.

9.4.6.2. Participant Population Analyses

Participant disposition, treatment status, demographics, baseline characteristics (that include year of birth, sex, race, and ethnicity), medical history, prior and concomitant

medications, study treatment exposure will be summarized descriptively and listed by participant. The participant's baseline characteristics may be used to derive differences (if any) between the pharmacokinetic parameters of different racial groups (e.g., Chinese, Japanese vs non-Asian) as per the request of regulatory bodies.

9.4.6.3. PK and PK-PD Analyses

Pharmacokinetics (PK) of GSK3228836 and nucleos(t)ide will be characterized. In all participants, Cτ and terminal half-life (t½) will be estimated. In participants with intensive PK sampling, GSK3228836 and nucleos(t)ide plasma PK parameters will be derived, including but not limited to AUC, Cτ, C_{max}, and tmax.

Population PK model: A Population PK model will be developed to describe the time-course of plasma PK of GSK3228836 in HBV patients. The data will be analyzed using nonlinear mixed effect modeling to estimate the PK parameters of GSK3228836 and the associated between-subject variabilities in addition to the residual variability. Covariate modeling and model qualification will be conducted. Additional details on the modeling process will be detailed in the population PK-PD analysis plan and the results will be reported separately.

PK-PD model: Various PK-PD relationships including PK-efficacy and PK-safety relationships will initially be explored graphically; if a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modeling will be conducted using nonlinear mixed effect methods. These models will characterize the exposure-response relationships and will define the factors (covariates) that may be predictors of efficacy and safety. Additional details of PK-PD analyses will be provided in the population PK-PD analysis plan and the results will be reported separately.

9.5. Interim Analyses

Three interim analyses are planned for the study in addition to regular IDMC safety reviews (See Section 9.6).

All interim analyses will be conducted separately for participants on stable nucleos(t)ide treatment and participants not currently on nucleos(t)ide therapy. Where possible, the interim analyses will be scheduled such that both populations are assessed at the same time. All interim analysis will be based on the ITT population.

The approximate timing, endpoint and criteria for each interim analysis are summarized in Table 12. The IDMC will review and approve the timing, endpoint and decision criteria for the planned interim analyses and the final approved framework will be included in the IDMC charter.

Additional interim analyses may be conducted after the third interim (at which time all participants will have completed treatment and sponsor staff [as specified in the blinding plan] will be unblinded), to support development planning and decision making. If conducted, these analyses will be unblinded to the sponsor staff (as specified in the blinding plan) and referenced in the clinical study report.

Table 12 Interim analysis timing, endpoint and decision rule

Interim	Timing	Endpoint	Decision Rule	Note
1	~ 30% participants complete Week 12	Week 12 response rate (≥0.5 log10 decline in HBsAg at Week 12)	Stop sub-population if all participants' Week 12 response rate is predicted to be very low	Arms 1 -3 combined
2	~ 50% participants complete Week 24	Week 24 response rate (HBsAg <LLOQ and HBV DNA <LLOQ at Week 24)	Stop sub-population if all participants' Week 24 response rate is predicted to be very low	Arms 1 &2 combined
3	All participants complete Week 24	Sustained virologic response rate (Primary endpoint)	The predicted end-of-study sustained virologic response rate will be modelled to support development plan decision making. No option to stop the trial at this point as all participants will have completed treatment.	

9.6. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will review ongoing unblinded safety data in this study and the planned interim analysis described in Section 9.5. The IDMC will meet on a regular basis as outlined in the charter. The IDMC/Review Board charter will describe the procedures related to IDMC operations in greater detail. For details on the IDMC, refer to Section 10.1.5.

The first data review meeting will be held approximately 18 weeks post first-subject-first-dose (the initial dry run will be blinded with a data cut at approximately 12 weeks post-first subject first dose [FSFD]). Thereafter, the frequency of scheduled meetings depends on subject enrolment, information accumulated and safety event rates but will occur approximately every 3 months. At the first meeting the IDMC may consider if the benefit risk assessment is acceptable to expand the ALT inclusion criterion threshold (from ALT<3xULN to <5xULN) for participants not receiving nucleos(t)ide therapy. Review of the ALT threshold will continue at each meeting as required.

9.7. Internal Safety Review Team (SRT)

A separate internal safety review team will meet to review all participants' blinded safety data on a regular basis.

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 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.
- 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), 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 legally authorized representative 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 GSK3228836 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3228836 approved for medical use or approved for payment coverage.

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 tick box 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.

10.1.5. Committees Structure

The overall responsibility of the IDMC, which consists of at least 2 physicians and 1 statistician, is to protect the ethical and safety interests of participants recruited into clinical studies while ensuring the scientific validity of the studies. The IDMC will meet at predefined times for each study, as well as ad hoc (as deemed appropriate), to evaluate the risk versus benefit of GSK3228836.

Specific responsibilities of the IDMC include:

1. Reviewing the IDMC Charter supplied by GSK and making any recommendations for changes to GSK; all IDMC members must approve and sign the Charter prior to enrolling the first participant into the study.
2. Determining the type of information needed for review of efficacy/safety data, as required, in the context of benefit/risk.
3. Recommending the format for the presentation of this information.
4. Reviewing data collection methods, safety/efficacy monitoring procedures and making recommendations for additions or adjustments to the trial design following interim analyses (IA).

GSK is responsible for the selection of IDMC members. The IDMC Chairperson may assist in selecting IDMC members. The skills and experiences necessary to properly fulfil the role of the IDMC (*e.g.*, relevant medical specialties) require careful consideration and have been pre-specified by GSK. In the event that a member is unable to continue participation on the IDMC, GSK, in conjunction with the IDMC Chairperson, will recommend a replacement. GSK has the final decision on the replacement. No substitution of members is permissible for individual meetings.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic 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.
- 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 (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.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.
- 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 Clinical Study Report (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.

- Quality tolerance limits (QTLs) 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 QTLs and remedial actions taken will be summarized in the clinical study report.

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 can be found in the RAP.

10.1.9. Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

GSK or its 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

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 participant 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the central laboratory. Local laboratory samples may still be collected as needed by the site.
- Local laboratory results are required for analysis of platelets during the dosing period, and be available for the investigator's review prior to dosing. A sample for central analysis is obtained at the same time
- Otherwise, local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - 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.

Table 13 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count[1] RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC count (with Differential if WBC abnormal): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total, indirect, and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum	Total Protein

Laboratory Assessments	**Parameters**			
			Glutamic-Pyruvic Transaminase (SGPT)	
	Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• By dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle-stimulating hormone and estradiol (as needed only) • Highly sensitive urine or serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Total bile acid • Serology (HIV antibody, hepatitis C virus antibody, and hepatitis D virus antibody) • Hepatitis B serology (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBsAg], hepatitis B e antigen [HBeAg], hepatitis B e antibody [anti-HBeAg], Hepatitis B virus DNA [HBV DNA], Hepatitis B virus RNA [HBV RNA], Hepatitis B core related antigen [HBcrAg]) • Other laboratory: PT, INR, activated partial thromboplastin time (aPTT), Alpha-fetoprotein, ANCA (MPO-ANCA, PR3-ANCA), APRI/Fibrosure, Complement factors C3, C4, and Bb, hs-CRP, MCP-1, angiopoetin II, PBMC, soluble protein, PAX Gene • Urine ACR • Optional collections: genetic sample • Viral Sequencing: HBV Genotype/phenotype, HBV DNA, HBV RNA All study-required laboratory assessments will be performed by a central laboratory, with the exception: • Platelet counts for investigator decisions may be drawn at local laboratory			
Additional tests listed under safety follow-up processes	**<u>Liver Chemistry Stopping Criteria</u>[3]** • Viral hepatitis serology including: o Hepatitis A IgM antibody; o Cytomegalovirus IgM antibody; o Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); o Hepatitis E IgM antibody			

Laboratory Assessments	Parameters
	○ Hepatitis B virus DNA load ○ Hepatitis C virus RNA load ○ Hepatitis D virus antibody • PK sample • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay
	Drug Induced Vascular Injury and Complement Stopping Criteria • CH50 • Factor B level • Factor H level • sC5b-9
	Hematological Stopping Criteria • anti-platelet antibodies
	Drug Induced Kidney Injury Stopping Criteria • 24-hour urine analysis • renal ultrasound • urine microscopy • serum urea and creatinine • platelets • urgent serum vasculitis screen [including ANCA, ANA, dsDNA, cryoglobulins • serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP) • complement panel (C3, C4, C5a and Bb)

NOTES :

1. Platelets will require local/central lab collection while participants are on-treatment; local lab will be optional for sites during the post-treatment period
2. Urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC or if urine testing is unavailable
3. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 7. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin >2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New 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 drug-drug 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.
- "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.

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).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- 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.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug 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 • 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 in the CRF. • 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 /AE/SAE CRF page.

- 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 assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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.

10.3.5. Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric Adverse Events

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

The DAIDS Table is available at the following link:

https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one

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 (IB) 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**.**
- 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.

10.3.6. 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- 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 by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and 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 not considered WOCBP

- 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.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt 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 enrollment.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner 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.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
• Sexual abstinence • *Note: 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.*
• **ACCEPTABLE METHODS[d]**
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with

	spermicide (double-barrier methods)[c]
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.
d.	Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.
e.	Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant 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) or still birth (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 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 GSK3228836 or CHB and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3228836 or other 2'-MOE 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 GSK3228836 or study interventions of this class. 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 GSK3228836 (or study interventions of this class) or CHB continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines

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:

- 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 C virus RNA load
- Hepatitis D virus antibody

- Obtain a blood sample for pharmacokinetic (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 Study Reference Manual (SRM).
    - Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
    - Fractionate bilirubin, if total bilirubin ≥ 1.5 X upper limit of normal (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 Adverse Event (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]), if available.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) or Liver biopsy to evaluate liver disease.
  - The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Intervention

Restart refers to resuming study intervention following liver stopping events in which there is a clear underlying cause (other than drug-induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

- Approval by GSK for study intervention restart can be considered where:
  - Investigator requests consideration for study intervention restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
  - Possible study intervention-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study intervention has a confirmed genetic marker associated with liver injury, the presence of the marker should be excluded. If study intervention-related liver injury cannot be excluded, the guidance on rechallenge will apply.
- There is no evidence of alcohol-related hepatitis.
- Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approval of study intervention restart (as required) has been obtained.

If restart of study intervention is approved by GSK Medical Governance in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study intervention administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart of study intervention. Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by GSK
- Participants approved by GSK for restart of study intervention must return to the clinic twice a week for liver function tests until stable liver function tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the participant meets protocol-defined liver chemistry stopping criteria after study intervention restart, study intervention should be permanently discontinued.
- The Medical Monitor, and the IRB/IEC, must be informed of the outcome for the participant following study intervention restart.
- GSK must be notified of any adverse events.

10.7. Appendix 7: Country-specific requirements

10.7.1. China

The following sections outline China-specific changes from the main protocol.

In China, collection of exploratory/biomarker labs will be contingent on agreements with China regulatory (HGRAC), otherwise the SoA should be the same as the main study protocol.

10.7.1.1. China Schedule of Activities

Table 14 Screening

ASSESSMENTS	
Informed Consent	X
Inclusion and exclusion criteria	X
Demography	X
Medical history (includes substance usage) and current medical conditions	X
Medication history and concomitant medication review	X
Full physical exam including height and weight	X
Vital signs	X
12-lead ECG	X
LABORATORY	
Serum hCG pregnancy test (women of child-bearing potential)	X
FSH/Estradiol (to confirm status of women of non-child-bearing potential)[1]	X
Hematology/Chemistry/Urinalysis	X
Urine ACR	X
PT, INR, aPTT	X
HIV, hepatitis D, and hepatitis C screen	X
Hepatitis B profile (HBsAg, HBV DNA, HBeAg)	X
Alpha-fetoprotein	X
APRI/Fibrosure	X
ANCA[2]	X
Total bile acid profile (as available)	X
Complement C3, C4, C5a, hsCRP, MCP-1, complement Bb, Ang-2	X

1. As appropriate to confirm menopause
2. With MPO-ANCA, PR3-ANCA if results are positive or border-line positive

Table 15 On Treatment Day 1 to Day 50

ASSESSMENTS[1]	**Day 1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
Window		±1 day			±3 days					
	Week 1	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
Randomization	X									
Study treatment dosing	X	X	X	X	X	X	X	X	X	X
Safety Assessments										
AE/SAE review	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Symptom directed exam	X						X			
Vital signs	X	X	X	X	X	X	X	X	X	X
Injection site reactions	X	X	X	X	X	X	X	X	X	X
Questionnaire (cell phone app, optional)	X									
Questionnaire (patient feedback on dosing regimen)	X									
Patient Reported Outcomes Questionnaires: HBQoL, EQ-5D	X									
Laboratory										
Pregnancy test (women of child bearing potential)[2]	X[2]						X			
Hematology[3] [includes platelet count and WBC]	X		X		X	X	X	X	X	X
PT, INR, aPTT	X						X			
Chemistry	X		X		X	X	X	X	X	X
Urinalysis	X		X		X	X	X	X	X	X
Urine ACR	X				X		X		X	
HBsAg and HBV DNA	X		X		X	X	X	X	X	X
Anti- HBsAg	X						X			
Anti-HBeAg	X						X			
HBeAg (only for participants HBeAg positive at screening)	X		X		X	X	X	X	X	X

ASSESSMENTS[1]	**Day 1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
Window		±1 day			±3 days					
	Week 1	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
HBV RNA, HBcrAg and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)	X					X				X
Complement C3, Complement C4, hs-CRP, MCP-1	X				X		X		X	
Complement C5a, Complement factor Bb	X				X		X		X	
ANCA, Ang II	X						X			
PK	X		X		X	X	X	X	X	X
PBMC Collection for immunophenotyping[4]	X									
Soluble Protein (immunology) [4]	X					X				X
PAXGene RNA for expression analysis in whole blood[4]	X									
OPTIONAL: Genetics[4]	X									
Archived Samples [serum; plasma]	X				X		X		X	

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM
2. A WOCBP must have both:
    a. A confirmed menstrual period prior to the first dose of study intervention; additional evaluation (e.g., amenorrhea in athletes, birth control) should also be considered
    b. AND a negative highly sensitive pregnancy test [urine or serum] within 24 hours before the first dose of study treatment
3. Hematology- platelet count to be analyzed at local laboratory prior to dose; hematology samples to be collected for central laboratory assessments in parallel
4. In China, collection of these labs will be contingent on agreements with China regulatory (HGRAC), and will be optional for Chinese participants

Table 16 On-Treatment: Day 57 to Day 162

Assessments[1]	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D120**	**D127**	**D134**	**D141**	**D148**	**D155**	**D162**
Window	**±3 days**															
	W9	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**
Study treatment dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom directed exam	X				X				X				X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Questionnaire (cell phone app; optional)																X
Questionnaire (patient feedback on dosing regimen)																X
Laboratory																
Pregnancy test (women of child bearing potential)	X				X				X				X			
Hematology[2] [includes platelet count, and WBC]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR	X		X		X		X		X		X		X		X	
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti- HBsAg	X				X				X				X			
Anti- HBeAg	X				X				X				X			
HBeAg (only for participants HBeAg positive at screening)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessments[1]	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D120**	**D127**	**D134**	**D141**	**D148**	**D155**	**D162**
Window	**±3 days**															
	W9	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**
HBV RNA, HBcrAg and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)				X				X				X				X
Complement C3, Complement C4, hs-CRP, MCP-1	X		X		X		X		X		X		X		X	
Complement C5a, Complement factor Bb	X		X		X		X		X		X		X		X	
ANCA, Ang II	X				X				X				X			
PK[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PBMC Collection for immunophenotyping[4]				X												X
Soluble protein (immunology) [4]				X				X				X				X
PAXGene RNA for expression analysis in whole blood[4]					X											
Archived Samples [serum; plasma]	X		X		X		X		X		X		X		X	

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM
2. Hematology- platelet count to be analyzed at local laboratory prior to dose; hematology samples to be collected for central laboratory assessments in parallel
3. In addition to the pre-dose sample Intensive PK collection may be collected for China, Japan, and country(ies) with participants of non-Asian heritage (TBD) See Table 8 for details of intensive PK sample collection

   Intensive PK (GSK3228836 and nucleos[t]ide) will be collected at one visit between Week 14 (inclusive) and Week 24 (inclusive) chosen between the site and participant: post dose at 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 8 hr, 12 hr, 24 hr, 72 hr, and 168 hr [the site should make all attempts to align the 168 hr post-dose PK with the next scheduled visit's pre-dose PK, see Table 8 for more details]
4. For China, collection of these labs will be contingent on agreements with China regulatory (HGRAC), and will be optional for Chinese participants

Table 17 Off-Treatment Follow-Up

Assessments[1]	**OT-Day 1**	**OT-Day 8**	**OT-Day 22**	**OT-Day 50**	**OT-Day 78**	**OT-Day 106**	**OT-Day 134**	**OT-Day 162**	**Early Termination**
Window	± 3 days		± 10 days						
	OT- W1	**OT-W2**	**OT-W4**	**OT-W8**	**OT-W12**	**OT-W16**	**OT-W20**	**OT-W24**	
Safety Assessments									
AE/SAE review	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X
Symptom directed exam	X	X		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes Questionnaire: HBQOL, EQ-5D								X	
Laboratory									
Pregnancy test (women of child bearing potential)	X		X	X	X	X	X	X	X
Hematology[2] [includes platelet count, and WBC]	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X		X		X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Urine ACR	X	X	X	X	X	X	X	X	X
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X
Anti- HBsAg	X	X	X	X	X	X	X	X	X
Anti- HBeAg	X	X	X	X	X	X	X	X	X
HBeAg (only for participants HBeAg positive at screening)	X	X	X	X	X	X	X	X	X
HBV RNA, HBcrAg and Sequencing (HBV Genotype/phenotype; HBV DNA and/or RNA)	X		X		X		X	X	X
Complement C3, Complement C4, hs-CRP, MCP-1		X	X	X	X	X	X	X	X
Complement C5a, Complement factor		X	X	X	X	X	X	X	X

Assessments[1]	**OT-Day 1**	**OT-Day 8**	**OT-Day 22**	**OT-Day 50**	**OT-Day 78**	**OT-Day 106**	**OT-Day 134**	**OT-Day 162**	**Early Termination**
Window	± 3 days		± 10 days						
	OT- W1	**OT-W2**	**OT-W4**	**OT-W8**	**OT-W12**	**OT-W16**	**OT-W20**	**OT-W24**	
Bb									
ANCA, Ang II	X		X	X	X	X	X	X	X
PK	X	X	X	X	X	X	X	X	X
PBMC Collection for immunophenotyping[3]	X				X			X	X
Soluble Protein (immunology)[3]	X		X		X		X	X	X
PAXGene RNA for expression analysis in whole blood[3]	X				X			X	X
APRI/Fibrosure								X	X
Archived Samples [serum; plasma]	X	X	X	X	X	X	X	X	X

1. In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the SRM
2. Hematology- platelet count analyzed at local laboratory is optional during the off-treatment period; hematology samples to be collected for central laboratory assessments (required; if local lab is being drawn, in parallel with local lab sample)
3. For China, collection of these labs will be contingent on agreements with China regulatory (HGRAC), and will be optional for Chinese participants

OT: off-treatment; the first off-treatment visit occurs 7 days after the last study treatment dose received, whether planned or last dose given after participant is withdrawn from study treatment (e.g., the planned first off-treatment visit occurs on Day 169, 7 days after the Day 162 visit; if participant is withdrawn from study treatment on Day 50, the first off-treatment visit occurs on Day 57)

10.7.1.2. China Biomarkers and Archived Samples

For China, collection of PBMCs, plasma protein, PAXgene RNA, and genetic samples will be contingent on agreements with China regulatory (HGRAC) and will be optional for Chinese participants. Depending on the agreements with China regulatory and ethics committees, all or some of these biomarkers will be made optional for Chinese participants.

Collection of samples for other biomarker research is part of this study. These exploratory biomarker samples will be collected to evaluate the pathogenesis of CHB; the absorption, distribution, metabolism, or excretion of GSK3228836; or the participant's response to GSK3228836. In addition, continuing research may identify other proteins, transcripts or biomarkers related to GSK3228836 treatment, the response to GSK3228836 or the pathogenesis of CHB, which will be evaluated in these samples.

- Blood samples, including serum, plasma, PBMCs and PAXgene tubes, will be collected to evaluate virologic and immune biomarkers related to the pathogenesis of CHB and the participant's response to GSK3228836. Samples will be collected according to the schedule described in the SoA and as detailed in the laboratory manual provided separately to sites.
- For China- stored samples (e.g., archived samples) may be used for the purposes of follow-up exploration of laboratory findings and/or AEs (e.g., see Section 7 for additional analyses in case of an AE or SAE).

10.8. Appendix 8: Abbreviations and Trademarks

ACR	albumin to creatinine ratio
AE	adverse event
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-platelet index
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BUN	blood urea nitrogen
CHB	chronic hepatitis B
CL/F	apparent subcutaneous plasma clearance
CKD-EPI	Chronic Kidney Disease Epidemiologic Collaboration
C_{max}	maximum observed concentration
Ct	concentration
CONSORT	consolidated standards of reporting trials
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
dL	deciliters
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ET	early termination
FSH	follicle stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
GSK	GlaxoSmithKline
H	hours
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B virus e-antigen
Anti- HBsAg	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HPLC	High performance liquid chromatography
HPF	high-power field
hs-CRP	high sensitivity C-reactive protein
IB	investigator's brochure
ICH	international conference on harmonisation
IDMC	Independent Data Monitoring Committee
IDO	indoleamine 2,3 dioxygenase
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
ISR	injection site reaction
ITT	intent-to-treat
IU	international units
Kg	kilograms
kPa	kilopascals

L	liters
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
m^2	square meters
MedDRA	medical dictionary for regulatory activities
Mg	milligrams
Min	minutes
mL	milliliters
mm^3	cubic millimeters
MOE	methoxyethyl
Msec	milliseconds
MSDS	material safety data sheet
NA	nucleos(t)ide analog
Ng	nanograms
Nucleos(t)ide	nucleoside or nucleotide
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics(s)
PEG	pegylated
PK	pharmacokinetic(s)
PT	prothrombin time
QTcF	Fridericia's QT correction formula
RAP	reporting and analysis plan
RBC	red blood cell
RNA	ribonucleic acid
RR	response rate
SAE	serious adverse event
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
SOP	standard operating procedure
SPEP	serum protein electrophoresis
SRM	study reference manual
SVR	sustained virologic response
$t_{½}$	terminal half-life
TCM	traditional Chinese medicine
t_{max}	time of maximum observed concentration
U	units
UA	urinalysis
μg	micrograms
ULN	upper limit of normal
UPEP	urine protein electrophoresis
μmol	micromole
WBC	white blood cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

10.9. Appendix 9: Protocol Amendment History

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

Amendment 01: 10-MAY-2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the Europe because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The primary drivers for this amendment were non-substantial changes, mostly for clarification and further directives due to the COVID-19 pandemic.

In addition, minor typographical errors and inconsistencies have been corrected and minor editorial changes have been made. Changes made to the text body have been made concurrently in the synopsis.

Section # and Name	Description of Change	Brief Rationale
Throughout, as appropriate	Changed the primary estimand text from: "sustained virologic response for 24 weeks after the end of GSK3228836 treatment in the absence of rescue medication.", to: "sustained virologic response for 24 weeks after the **planned** end of GSK3228836 treatment in the absence of rescue medication."	Some participants may withdraw from treatment early, the word "**planned**" has been added to clarify that for the primary estimand, SVR is assessed 24 weeks after the planned end of treatment, not the actual end of treatment.
Throughout, as appropriate	Changed subject to participant.	Current guidelines.
Schedule of Activities tables, all and Section 8.2.1 Physical Examinations	Changed brief physical exam to symptom directed exam.	Updated to reflect risk reduction practices in limiting physical contact due to COVID-19 and to align with assessment covered by home nursing licenses.
Schedule of Activities tables, as required and applicable text throughout	Added *phenotype* for HBV RNA, HBcrAg, and Sequencing (HBV Genotype/*phenotype*; HBV DNA and/or RNA).	To provide clarity that sequencing will also be used to understand HBV phenotype.
Schedule of Activities tables, as required	Added footnote (only for selected sites able to transport to the analysis lab within the timeframe specified in the SRM) to entry for PBMC collection for immunophenotyping.	To allow flexibility for sites that are not equipped to transport the PBMC samples in a timely fashion.
Schedule of Activities, Table 4 and Table 17 (China)	Remove optional genetics sample from the Off-treatment follow-up visits in the Schedule of Activities.	Genetics sampling is only required at Day 1. The off-treatment follow-up sample was included in error.
Section 2.3.1.1	Added section titled Regarding COVID-19.	To inform of (no known additional)

Section # and Name	Description of Change	Brief Rationale
		risk of COVID-19 for HBV participants.
Section 3 Key Objectives and Estimand/Endpoints table and Section 9.4.2.2	A supplementary estimand for the primary endpoint was added.	Some participants may withdraw from treatment early, a supplementary estimand that assesses SVR 24 weeks after the actual end of treatment is included to support the primary objective.
Section 3 Key Objectives and Estimand/Endpoints table and Section 9.4.4.1 Estimands for Secondary Objective	Secondary Efficacy Endpoints: moved HBe-antibody (anti-HBeAg) levels from a continuous variable to a categorical variable.	Correction.
Section 3 Key Objectives and Estimand/Endpoints table and Section 9.4.4.1 Estimands for Secondary Objective	Secondary Efficacy Endpoints; Population summary: changed statistical estimator from Kaplan-Meier to Turnbull.	Given the data will be interval-censored, Turnbull's method is more appropriate than Kaplan-Meier method.
Section 3 Key Objectives and Estimand/Endpoints table	Secondary Efficacy Endpoints; Pharmacokinetics: removed PK derivations for apparent plasma clearance and apparent subcutaneous plasma clearance for GSK3228836 and apparent oral plasma clearance for nucleos(t)ide.	Apparent plasma clearance = Dose/AUC, with DOSE being constant, "apparent plasma clearance" reflects the same PK characteristics as AUC, thus redundant and can be removed.
Section 3 Estimand/Endpoints corresponding to Exploratory PK-PD relationships	Exploratory PK-PD endpoints changed from descriptive statistical summaries to PK-PD model dependent parameter outputs as endpoints.	Correction.
Section 5.2 Exclusion Criteria	Medical Conditions Number 3: provide clarity that liver biopsy and stiffness are historical measurements.	Provide clarity to investigators that these are for historical measurements, if available, not to be performed for assessment.
Section 5.2 Exclusion Criteria	Medical Conditions Number 8: ANCA	Updated to provide clear parameters for exclusion.
Section 5.2 Exclusion Criteria	Medical Conditions Number 9: C3	Updated to provide clear parameters for exclusion.
Section 6.5.2 Initiation of Nucleos(t)ides During GSK3228836 Treatment	Allowing for use of NA therapy in Arm 4 of the study (after the NA-restriction period, while on active GSK3228836), if there is concern about developing resistance to GSK3228836.	Updated to provide clarity as participants in Arm 4 do not start GSK3228836 until after Week 12.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4 Prohibited Medications and Non-Drug Therapies	Addition of anticoagulation therapies.	To make clear that anti-coagulation therapy is a prohibited medication as per the exclusion criteria.
Table 6 Liver Monitoring and Stopping Criteria	Updated to include discussions with Medical Monitor and clarification for taking patients off hold, as the terminology of "restart" should be used for the re-start criteria after a patient is permanently discontinued from treatment.	Clarification.
Section 7.1.1 Liver Chemistry Monitoring and Stopping Criteria	Added twice (in bold): Participants must be monitored **twice** weekly until liver chemistry abnormalities (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize, or return to within baseline values.	Corrected to align with the monitoring plan in Table 6.
Section 7.1.1 Liver Chemistry Monitoring and Stopping Criteria	Added text: 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.	To clarify and identify instance where medical monitor should be consulted.
Section 7.1.1 Liver Chemistry Monitoring and Stopping Criteria	Updated to include clarification that clinically significant lab changes should be confirmed, to correct Liver Events CRF to Liver Alcohol CRF.	Clarification/correction.
Section 7.1.1 Liver Chemistry Monitoring and Stopping Criteria	Clarify that the 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) should be conducted if available.	Serum acetaminophen adduct high performance liquid chromatography assay may not be available in all countries.
Section 7.1.3 Haematological Stopping Criteria	Added text (in bold): If the platelet count is uninterpretable or **a decreasing trend is noted** below LLN reference range, re-check the platelet counts as soon as possible **(the investigator may, at their discretion, opt to have the participant come to their next scheduled visit OR ask the participant to come earlier than their scheduled visit, as they feel appropriate based on review of the participant's clinical presentation and laboratory results).**	Clarification and to provide guidance to investigator.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.4 Drug Induced Kidney Injury (Renal) Stopping Criteria	Treatment Hold/Treatment Discontinuation changed baseline to pre-dose range for ACR and eGFR changes.	Clarification. The investigator may take into account natural fluctuations, as may be seen in the pre-dose screening or Day 1 values, in assessing changes in these parameters for the hold/stopping criteria.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Updated timing for recording AE/SAE as related to informed consent/dose administration.	Clarification.
9.4 Statistical Analysis	Updated all sections to provide clarity that statistical summaries and analyses will be conducted separately for the 2 population (on nucleos(t)ide treatment and not currently on nucleos(t)ide treatment).	Clarification.
Section 9.4.3 Primary Analyses	Amended specification of Bayesian model.	Model specification was amended to improve clarity and avoid repetition.
Table 11	Updates to clarify stratification factors for the 4 stratum.	Clarification/Correction.
Table 13	Changed SAE reporting bilirubin <2X ULN to >2X ULN.	Correction, due to typo.
Section 9.4.6.3 PK and PK-PD Analyses	Added description of Population PK model, removed efficacy and safety assessments (described in Objective/Endpoints).	Correction. Exploratory graphical analyses will be initially performed for efficacy and safety endpoints. Only If a relationship (exposure and efficacy and/or safety endpoints) is present will further modeling be conducted.
Section 9.6 Independent Data Monitoring Committee (IDMC)	Additional text added around IDMC safety reviews and IDMC review of ALT criteria.	Updated to describe the planned safety reviews and to provide clarity around when IDMC would review safety data to expand ALT inclusion criteria for treatment naïve participants and for participants who are not currently receiving treatment.
Section 10.3.5 Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric Adverse Events	Removed criteria that are contained within the DAIDs table.	Correction.
Section 10.6 Appendix 6	Added re-start guidelines.	Re-start guidelines were presented in Section 7.1.5 but were not included in the appendices.
Section 10.7.1	Corrected China Schedule of Activities, previously addressed in China-specific amendment.	To align with global Schedule of Activities.

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