TITLE PAGE

Protocol Title: B-Fine: An open label, single arm study to mechanistically interrogate the therapeutic effect of GSK3228836 in patients with Chronic Hepatitis B via intrahepatic immunophenotyping

Protocol Number: 212602/Amendment 01

Compound Number GSK3228836

Brief Title: A mechanistic study of GSK3228836 with fine needle aspiration (FNA) in Participants with Chronic Hepatitis B

Study Phase: PHASE IIA

Acronym: B-Fine

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: 122685

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Approval Date: 15-MAR-2021

SPONSOR SIGNATORY:

Protocol Title: B-Fine: An open label, single arm study to mechanistically interrogate the therapeutic effect of GSK3228836 in patients with Chronic Hepatitis B via intrahepatic immunophenotyping

Protocol Number: 212602/Amendment 01

Dickens Theodore, MD Senior Director, Clinical Development, Infectious Diseases, GlaxoSmithKline	**Date**

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**	**DNG Number**
Amendment 01	15-MAR-2021	TMF-11822142
Original Protocol	29-MAY-2020	2020N434303_00

Amendment 01 15-MAR-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:

CCI [redacted]

Other key changes include:

- a description of the risk of Covid-19 infection in the hepatis B population, added at the request of the Medicines & Healthcare products Regulatory Agency (MHRA).
- an update to the time to maximum alanine aminotransferase (ALT) analysis method.
- additional guidance and clarity for Investigators has been added.
- corrections to visit windows and visit numbering in the schedule of activities (SoA).

In addition, minor typographical errors and inconsistencies have been corrected and minor editorial changes have been made.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis: Key Objectives and Endpoints	HBe antibody (anti-HBeAg) levels have been re-classified as a categorical variable (previously a continuous variable)	This corrects an error in the original protocol.
	The analysis method for the time to maximum ALT has been updated from Kaplan-Meier to Turnbull	As visit spacing gets longer over time, interval censored method is more appropriate.
Section 1.3: Schedule of Activities	The Day 11 visit window was been updated from ±3 days to ±1 day	Updated to avoid potential overlap of the Day 8 and Day 11 visits
	Collection of PBMC samples for immunophenotyping updated from "Baseline, **Day 8 (Week 2)**, **Day 15 (Week 3)**, Day 29 (Week 5), **Day 85 (Week 13), Day 162 (Week 24),** Day 246 (Week 36) and Early Withdrawal" to "Baseline, Day 29 (Week 5), Day 246 (Week 36) and Early Withdrawal."	Amended to reduce sampling timepoints due to increased blood volume required for PBMC analysis.

Section # and Name	Description of Change	Brief Rationale
	The description of the standard examination has been updated from brief physical exam to symptoms directed exam	Updated to reflect risk reduction practices in limiting physical contact due to COVID-19 and to align with assessments covered by home nursing licenses.
	Clarification has been added that PK sample should be collected pre-dose.	This corrects an error in the original protocol.
	Guidance has been added that a fine needle aspiration (FNA) sample not to be collected if the participant has already withdrawn from treatment	Updated to reduce burden on participants who no longer wish to continue study treatment.
	A urine or serum pregnancy test has been added as an optional assessment at Day 1	Added for instances where the Screening serum human chorionic gonadotrophin (hCG) pregnancy test was >24 hours pre-dose first dose.
	The Week 28, 32 and 36 day numbers have been updated to Day 190, 218 and 246, respectively.	This corrects an error in the original protocol.
	The collection of samples for genetic resource have been removed from the SoA at all timepoints other than Week -1 (Baseline)	This corrects an error in the original protocol.
Section 2.3.1: Risk Assessment	Additional text added on risk with COVID-19 infection	Provide description of risk of COVID-19 infection in hepatitis B population
Section 2.3.3 Overall Benefit: Risk Conclusion	Additional text added on benefit/risk with COVID-19 infection	Include COVID-19 risk in the overall benefit:risk assessment
Section 3: Objectives and Endpoints	HBe antibody (anti-HBeAg) levels have been re-classified as a categorical variable (previously a continuous variable)	This corrects an error in the original protocol.
	The analysis method for the time to maximum ALT has been updated from Kaplan-Meier to Turnbull	As visit spacing gets longer over time, interval censored method is more appropriate. Turnbull method chosen, and this is consistent with Study 209348 (B-Together).
	Immunophenotyping added to list of possible measures for markers of immune cell function	To further expand the list of potential measures which may be used in the investigation of immune cell function.
Section 5.2 Exclusion Criteria	Exclusion criteria 8 and 9 have been re-written	Re-written following a request for clarification following protocol review by the MHRA.
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	Additional text added on bias mitigation	Updated to include reference to the blinding plan
Section 6.8.2 Prohibited Medications and Non-Drug Therapies	Included anti-coagulation therapies as prohibited medication and non-drug therapies	To be consistent with exclusion criteria

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1: Liver Chemistry Monitoring and Stopping Criteria	Additional text added in 'Bold' • Any **clinically significant** deterioration from the baseline in the liver parameters must be confirmed by retesting ALT, total bilirubin, direct bilirubin, and INR (if available). • **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 drug-induced liver injury (DILI) or the participant may continue with dosing.**	To clarify and identify instances where advice from the medical monitor should be sought
Section 7.1.3: Haematological Stopping Criteria	Additional text added around haematological stopping criteria	Updated to provide additional clarity.
Section 7.1.5: Study Intervention Restart or Rechallenge after Stopping Criteria Met	Added text in '**Bold**' as follows: Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approval of study intervention restart has been obtained **(if required).**	This corrects an error in the original protocol.
Section 8.2.1: Physical Examinations	Description of post-baseline brief physical examination updated to symptoms directed examination	Updated to reflect risk reduction practices in limiting physical contact due to COVID-19 and to align with assessments covered by home nursing licenses.
Section 8.2.3: Vital Signs	Requirement for vital sign measurement in a semi-supine position removed.	Updated as not required.
Section 9.4.4: Secondary Endpoint(s)	HBe antibody (anti-HBeAg) changed from a continuous to a categorical variable	This is to represent the data which have received since the start of the study.
	The analysis method for the time to maximum ALT has been updated from Kaplan-Meier to Turnbull	As visit spacing gets longer over time, interval censored method is more appropriate.
Section 9.6: Independent Data Monitoring Committee (IDMC)	Additional detail added regarding the timing of IDMC safety reviews	Updated to describe the planned safety reviews
Section 10.2: Appendix 2 Clinical Laboratory Tests	Additional text regarding processing of PBMC samples	Updated to allow for local laboratory processing of PBMC samples.
	Bilirubin SAE reporting requirements updated from $\leq$2xULN to $\geq$2xULN	To correct an error in the definition.
Section 10.6: Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines	Added text in '**Bold**' as follows: Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approval of study intervention restart has been obtained **(if required).**	This corrects an error in the original protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title:

B-Fine: An open label, single arm study to mechanistically interrogate the therapeutic effect of GSK3228836 in patients with Chronic Hepatitis B via intrahepatic immunophenotyping

Rationale:

B-Fine is an exploratory study of the therapeutic mechanism of GSK3228836 in participants with chronic hepatitis B (CHB) on stable nucleos(t)ide therapy. The study will investigate the virologic and immunologic correlates of HBsAg loss observed in participants when treated for 12 weeks with 300 mg GSK3228836. Repeat fine needle aspirates of the liver will be performed to enable analysis of liver-resident immune cells to investigate any immunomodulatory properties of GSK3228836 and to study the biology of underlying treatment-associated liver flares. Longitudinal analyses of blood-borne inflammatory signatures and virological assessments of CHB infection will be performed in parallel.

Key Objectives and Endpoints:

Objectives	Estimands/Endpoints
Primary	
Efficacy: To assess the effect of 12 weeks of GSK3228836 on serum hepatitis B virus surface antigen (HBsAg) levels in participants with CHB	The Primary Estimand supporting the primary objective of the study is defined as: • Population: Participants with CHB who receive at least one dose of investigational product (IP) • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variable: Achieving serum HBsAg level <lower limit of quantitation (LLOQ) at any time point up to and including Week 12 without the use of pegylated (PEG)-interferon or other immunomodulator therapies • Population-level summary: Percent of participants that achieve serum HBsAg level <LLOQ • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The primary estimand is the percentage of participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) who achieve serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP or adherence to IP.

Objectives	Estimands/Endpoints
Secondary	
Efficacy: To assess sustainability of serum HBsAg loss by GSK3228836 for up to 24 weeks off-treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment ▪ HBsAg from Week 13 to Week 36 will be used to assess sustained HBsAg response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment ▪ HBsAg for 24 weeks after end of actual treatment will also be used to assess sustained HBsAg response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies.
Efficacy: To assess sustainability of serum HBsAg and HBV DNA loss by GSK3228836 for up to 24 weeks off treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: o Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. ▪ HBsAg and HBV DNA from Week 13 to Week 36 will be used to assess sustained virologic response after the planned end of GSK GSK3228836 treatment. o Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies ▪ HBsAg and HBV DNA for 24 weeks after end of actual treatment will be used to assess sustained virologic response after the actual end of GSK3228836 treatment. • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies.

Objectives	Estimands/Endpoints
Efficacy: To assess the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses	Estimands supporting the secondary objective of assessing the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Intercurrent events: Discontinuation of, interruption of, adherence to IP will be ignored (treatment policy). PEG-interferon or other immunomodulator therapies will be handled with hypothetical strategy. 1) Categorical Variables: • Achieving: o HBsAg <LLOQ over time o HBV DNA <LLOQ over time o HBsAg and HBV DNA <LLOQ over time • Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log_{10} IU/mL) over time. • ALT>3X ULN at over time • HBe antibody (anti-HBeAg) levels over time Population summary: percentage of participants in each category. 2) Continuous Variables: • Actual values and change from baseline over time for HBsAg and HBV DNA • HBs antibody (anti-HBsAg) levels over time • Area under the curve (AUC) for ALT on treatment (12 weeks), during follow up (24 weeks), and on treatment + follow up (36 weeks). Population summary: mean values and/or mean changes from baseline for each variable 3) Time to Event Variable • Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks of treatment + follow up Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN) The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) are the population summary for each variable in the absence of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP, or adherence to IP.

Overall Design:

This study is a Phase IIa, multi-centre open label exploratory study of the therapeutic mechanism of GSK3228836 in participants with HBeAg-negative CHB on stable nucleos(t)ide therapy using repeat fine needle aspirations of the liver for intrahepatic immunophenotyping.

The study consists of a single treatment arm

1. 300 mg GSK3228836 for 12 weeks (loading schedule on Day 4 and Day 11). Participants will continue to receive their stable nucleos(t)ide therapy.

After the 12 weeks of dosing with GSK3228836, there will be a post-treatment follow-up period of 24 weeks.

Brief Summary:

The purpose of this study is to determine the therapeutic mechanism of GSK3228836 in participants with CHB. Study details include:

Study Duration: 37 weeks (45 weeks if include screening and flexible visit windows)

Treatment Duration: 12 weeks

Visit Frequency: Twice a week for the first 2 weeks, once a week through Week 14, once at Week 16, and once every 4 weeks thereafter

Study Hypothesis: GSK3228836 treatment will result in phenotypic changes in intrahepatic immunity associated with loss of HBsAg and treatment-emergent changes in ALT

Health Measurement/Observation: HBsAg <LLOQ

Number of Participants:

The study will enrol approximately 20 participants, but no more than 24.

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 and eligibility process. 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:

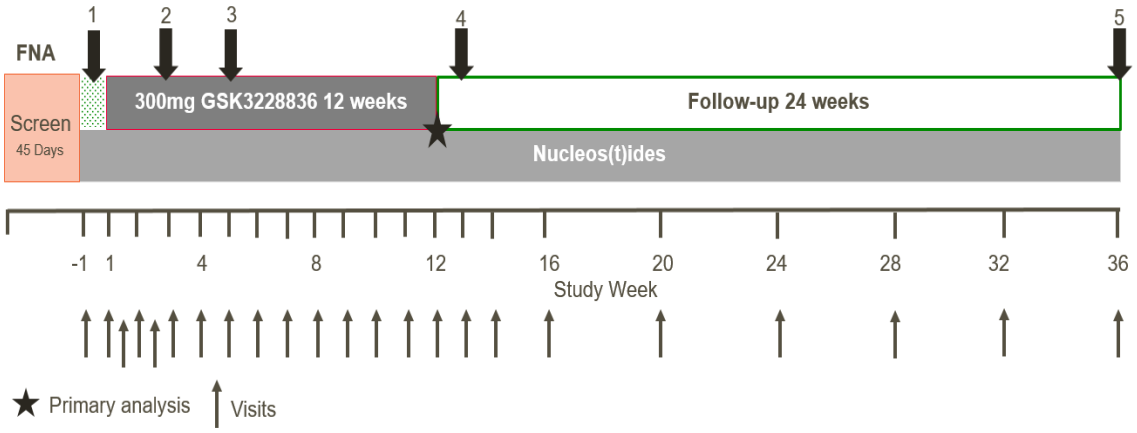
The total duration of the study, including screening, treatment and post-treatment follow-up, is not expected to exceed 45 weeks.

- 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
- Up to 1 week of pre-treatment assessments (including baseline FNA)
- 12 weeks treatment with GSK3228836
- 24 weeks post treatment follow-up (+ up to 10 days)

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

Data Monitoring/ Other Committee: Yes

1.2. Schema



An optional 6th FNA may be included between Weeks 6 and 36 following discussion between investigator and medical monitor.

1.3. Schedule of Activities (SoA)

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. Home visits may include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the study reference manual (SRM).

Table 1 Screening

ASSESSMENTS (45 Day window)	
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 ASSESSMENTS	
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/Fibrotest	X
ANCA[2]	X
Complement C3, C4, C5a, hsCRP, MCP-1, complement Bb, Ang-II	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 -7 to Day 50

Assessments	**Day -7 to Day -1**	**D1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
	Week-1 (Baseline)	**W1**	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
Window		±1 day				± 3 days					
Study treatment dosing[1]		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
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Symptoms directed exam	X	X						X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions		X	X	X	X	X	X	X	X	X	X
Laboratory											
Pregnancy test (women of child bearing potential)[2]	X							X			
Hematology[3][includes platelet count and WBC]	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
Urinalysis	X	X		X		X	X	X	X	X	X
Urine ACR	X	X				X		X		X	
HBsAg and HBV DNA	X	X		X		X	X	X	X	X	X
Anti-HBsAg	X							X			
Anti-HBeAg	X							X			
HBV RNA, HBcrAg, and sequencing (HBV genotype/phenotype, HBV DNA and/or RNA)	X					X	X	X			X
Complement C3, Complement C4, hs-CRP, MCP-1	X	X				X		X		X	
Complement C5a, Complement factor Bb	X	X				X		X		X	
ANCA, Ang II	X	X						X			
PK[4]		X		X		X	X	X	X	X	X
Fine needle aspiration of liver[5]	X					X[6]		X[6]			
PBMC Collection for immunophenotyping	X							X			
Soluble Protein	X			X		X	X	X			X
PAXGene RNA for expression analysis in whole blood	X			X		X		X			
Genetics	X										
Archived samples [serum; plasma]	X			X		X		X		X	

Assessments	**Day -7 to Day -1**	**D1**	**D4**	**D8**	**D11**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**
	Week-1 (Baseline)	**W1**	**W1**	**W2**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
Optional Assessments											
Urine or serum pregnancy test[7]		X									
Optional: fine needle aspiration of liver[8]									X	X	X
Optional: PBMC Collection for immunophenotyping[9]									X	X	X
Optional: Soluble Protein[9]									X	X	X
Optional: PAXGene RNA for expression analysis in whole blood[9]									X	X	X

1. Dosing to occur only after the completion of all assessments to determine dosing is safe to proceed
2. Women of childbearing potential (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] 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. PK samples are to be taken pre-dose
5. FNA will only be collected if the investigator deems it appropriate
6. Within 3 hours after study treatment dosing in Week 3 and Week 5. Sample not to be collected if the participant has already withdrawn from treatment.
7. Only to be conducted for women of child-bearing potential if the Screening serum hCG pregnancy test was >24 hours pre-dose first dose.
8. An optional additional FNA may be collected anytime between Week 6 and Week 36 following discussion between investigator and medical monitor based on unexpected changes in HBsAg or ALT. Only 1 additional FNA may be collected for each participant.
9. Only to be collected if the optional FNA is collected at this visit and has not already been collected as part of the standard assessments.

Table 3 On-Treatment Day 57 to Day 78

Assessments	**D57**	**D64**	**D71**	**D78**
	W9	**W10**	**W11**	**W12**
Window	± 3 days			
Study treatment dosing	X	X	X	X
Safety Assessments				
AE/SAE review	X	X	X	X
Concomitant medication review	X	X	X	X
Symptoms directed exam	X			
Vital signs	X	X	X	X
Injection site reactions	X	X	X	X
Laboratory				
Pregnancy test (women of child bearing potential)	X			
Hematology[1] [includes platelet count and WBC with differential]	X	X	X	X
PT, INR, aPTT	X			
Chemistry	X	X	X	X
Urinalysis	X	X	X	X
Urine ACR	X		X	
HBsAg and HBV DNA	X	X	X	X
Anti-HBsAg	X			
Anti-HBeAg	X			
HBV RNA, HBcrAg, and Sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)				X
Complement C3, Complement C4, hs-CRP, MCP-1	X		X	
Complement C5a, Complement factor Bb	X		X	
ANCA, Ang II	X			
PK[2]	X	X	X	X
Soluble Protein				X
Archived samples [serum; plasma]	X		X	
Optional Assessments				
Optional: fine needle aspiration of liver[3]	X	X	X	X
Optional: PBMC Collection for immunophenotyping[3]	X	X	X	X
Optional: Soluble Protein[4]	X	X	X	X
Optional: PAXGene RNA for expression analysis in whole blood[4]	X	X	X	X

1. Hematology- platelet count to be analyzed at local laboratory prior to dose; hematology samples to be collected for central laboratory assessments in parallel
2. PK samples are to be taken pre-dose.
3. An optional additional FNA may be collected anytime between Week 6 and Week 36 following discussion between investigator and medical monitor based on unexpected changes in HBsAg or ALT. Only 1 additional FNA may be collected for each participant.
4. Only to be collected if the optional FNA is collected at this visit and has not already been collected as part of the standard assessments.

Table 4 Off-Treatment Follow-Up Day 85 to Day 246

Assessments	**Day 85**	**Day 92**	**Day 106**	**Day 134**	**Day 162**	**Day 190**	**Day 218**	**Day 246**	**Early Termination**
	W 13	**W 14**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**NA**
Window	± 3 days		± 10 days						
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
Symptoms 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[1] (includes platelet count, and WBC with differential)	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X	X	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
HBV RNA, HBcrAg, and Sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)	X		X		X	X	X	X	X

Assessments	**Day 85**	**Day 92**	**Day 106**	**Day 134**	**Day 162**	**Day 190**	**Day 218**	**Day 246**	**Early Termination**
	W 13	**W 14**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**NA**
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	X	X	X	X
PK	X	X	X	X	X	X	X	X	X
Fine Needle Aspiration of Liver[2]	X							X	X
PBMC Collection for immunophenotyping								X	X
PAXGene RNA for expression analysis in whole blood	X				X			X	X
Soluble Protein	X		X		X		X	X	X
APRI/Fibrosure								X	X
Archived Samples [serum; plasma]	X	X	X	X	X	X	X	X	X
Optional Assessments									
Optional: fine needle aspiration of liver[3]		X	X	X	X	X	X		
Optional: PBMC Collection for immunophenotyping[4]		X	X	X	X	X	X		
Optional: Soluble Protein[4]		X	X	X	X	X	X		
Optional: PAXGene RNA for expression analysis in whole blood[4]		X	X	X	X	X	X		

1. Hematology- platelet count analyzed at local laboratory is **optional** during the off-treatment period; hematology samples to be collected for central laboratory assessments
2. FNA will only be collected if the investigator deems it appropriate
3. An optional additional FNA may be collected anytime between Week 6 and Week 36 following discussion between investigator and medical monitor based on unexpected changes in HBsAg or ALT. Only 1 additional FNA may be collected for each participant.
4. Only to be collected if the optional FNA is collected at this visit and has not already been collected as part of the standard assessments.

2. INTRODUCTION

2.1. Study Rationale

B-Fine is an exploratory study of the therapeutic mechanism of GSK3228836 in participants with HBeAg-negative CHB on stable nucleos(t)ide therapy. The study will investigate the virologic and immunologic correlates of HBsAg loss observed in participants when treated for 12 weeks with GSK3228836. Repeat fine needle aspirates of the liver will be performed to enable analysis of liver-resident immune cells to investigate any immunomodulatory properties of GSK3228836 and to study the biology of underlying treatment-associated liver flares. Longitudinal analyses of blood-borne inflammatory signatures and virological assessments of CHB infection will be performed in parallel.

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) and serum HBV DNA [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 HBsAg (so called non-infectious "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 (cccDNA) 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. GSK3228836 treatment permits examination of whether reduction of HBsAg allows resumption of a host immune response against HBV and infected cells and can suppress serum HBsAg to <LLOQ. GSK3228836 has been designed and selected to minimize risk of proinflammatory response associated as a class effect by methylating every cytosine in the ASO sequence as well as avoiding the presence of CpG motifs that can be recognized by pattern recognition receptors [Henry, 2008]. However, it is expected that GSK3228836 may trigger marginal immune activation in the local environment of the liver, which may not be readily detectable in periphery. In turn, the intrinsic immunostimulatory activity of GSK3228836 may contribute to the efficacy in addition to direct pharmacodynamic response of HBsAg reduction [Yuen, 2019].

Recently, a functional cure of CHB infection has been endorsed as the endpoint for new HBV therapies [Kim, 2018]. Functional cure of CHB infection is defined as sustained

suppression of serum HBsAg to <LLOQ (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.

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, drug induced vascular inflammation (DIVI), hematology, renal function, and PK are discussed in Section 7.

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 oligonucleotides (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 inflammation **Stopping Criteria:** Proposed Monitoring Schedule and Stopping Rules for Drug Induced Vascular Inflammation 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 7 **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.

Regarding 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 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	Estimands/Endpoints
Primary	
Efficacy: To assess the effect of 12 weeks of GSK3228836 on serum HBsAg levels in participants with CHB	The Primary Estimand supporting the primary objective of the study is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variable: Achieving serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies • Population-level summary: Percent of participants that achieve serum HBsAg level <LLOQ • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The primary estimand is the percentage of participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) who achieve serum HBsAg level <LLOQ at any time point up to and including Week 12, without the use of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP or adherence to IP.
Secondary	
Efficacy: To assess sustainability of serum HBsAg loss by GSK3228836 for up to 24 weeks off-treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment ▪ HBsAg from Week 13 to Week 36 will be used to assess sustained HBsAg response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment ▪ HBsAg for 24 weeks after end of actual treatment will also be used to assess sustained HBsAg response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies.

Objectives	Estimands/Endpoints
Efficacy: To assess sustainability of serum HBsAg and HBV DNA loss by GSK3228836 for up to 24 weeks off treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: o Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment ▪ HBsAg and HBV DNA from Week 13 to Week 36 will be used to assess sustained virologic response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. o Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment ▪ HBsAg and HBV DNA for 24 weeks after end of actual treatment will be used to assess sustained virologic response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies.
Efficacy: To assess the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses	Estimands supporting the secondary objective of assessing the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Intercurrent events: Discontinuation of, interruption of, adherence to IP will be ignored (treatment policy). PEG-interferon or other immunomodulator therapies will be handled with hypothetical strategy. 1) Categorical Variables: • Achieving: o HBsAg <LLOQ over time o HBV DNA <LLOQ over time o HBsAg and HBV DNA <LLOQ over time • Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL) over time. • ALT>3X ULN at over time • HBe antibody (anti-HBeAg) levels over time Population summary: percentage of participants in each category. 2) Continuous Variables: • Actual values and change from baseline over time for HBsAg and HBV DNA

Objectives	Estimands/Endpoints
	• HBs antibody (anti-HBsAg) levels over time • Area under the curve (AUC) for ALT on treatment (12 weeks), during follow up (24 weeks), and on treatment + follow up (36 weeks). Population summary: mean values and/or mean changes from baseline for each variable 3) Time to Event Variable • Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks of treatment + follow up Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN) The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) are the population summary for each variable in the absence of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP, or adherence to IP.
Safety	
Safety: To assess the safety and tolerability of GSK3228836 when dosed for 12 weeks in participants with CHB	Clinical assessments including, but not limited to vital signs, laboratory measurements and adverse events
Exploratory	
CCI [redacted]	

Objectives	Estimands/Endpoints
CCI	

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase IIa, multi-centre open label exploratory study of the therapeutic mechanism of GSK3228836 in participants with HBeAg-negative CHB on stable nucleos(t)ide therapy using repeat fine needle aspirations of the liver for intrahepatic immunophenotyping (see Section 1.2).

The study consists of a single treatment arm:

1. 300 mg GSK3228836 for 12 weeks (loading schedule on Day 4 and Day 11). Participants will continue to receive their stable nucleos(t)ide therapy.

After the 12 weeks of dosing with GSK3228836, there will be a post-treatment follow-up period of 24 weeks. An Independent Data Monitoring Committee (IDMC) will review the data (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

The overall objective of the study is to investigate the therapeutic mechanism of GSK3228836 in the liver using repeat fine needle aspirates to phenotype changes in intrahepatic immunity that are associated with loss of HBsAg and treatment-emergent changes in ALT.

Understanding the interplay between the virology of CHB and the host immune system will be key to the rational, evidence-based selection of biomarkers of response, optimisation of therapeutic approaches and selection of combination treatment regimens [Gill, 2019].

Study ISIS 505358-CS3 has already demonstrated efficacy of up to 4 weeks treatment with GSK3228836 on serum HBsAg levels in treatment naïve and nucleos(t)ide-controlled participants, with concomitant reversible elevations in serum ALT, believed to be indicative of HBV-targeted immune responses against infected hepatocytes.

Additional comprehensive investigation of the mechanism of action of GSK3228836 in the liver compartment is essential:

- To determine whether GSK3228836 has an immunomodulatory mechanism of action in addition to its previously described direct antiviral effects on HBV mRNA.
- To investigate the relationship between GSK3228836-mediated suppression of HBsAg, ALT flares and the potential for functional cure.
- To investigate immunological and/or virological correlates of HBsAg-suppression that may enable future response-guided therapy.
- To identify novel immunological pathways or targets with the potential to improve functional cure rates when used in combination or sequence with GSK3228836.

Study 212602 (B-Fine) will investigate 12 weeks treatment with 300 mg/week GSK3228836 (including loading doses on Day 4 and Day 11 used in Study ISIS 505358-CS3).

Rationale for study population

In study 212602 (B-Fine), participants expected to have the highest chance of achieving HBsAg level <LLOQ with 12 weeks of treatment with GSK3228836 will be enrolled. The following criteria have been included to aid selection of the optimal population to best study intrahepatic and peripheral virological and immunological correlates of HBsAg loss and treatment-emergent ALT elevations.

- Patients on stable nucleos(t)ide therapy
- Patients who are HBeAg-negative

Selection of nucleos(t)ide-controlled CHB patients

Efficacy of 4 weeks treatment with GSK3228836 has been investigated in Phase IIa study, ISIS 505358-CS3, in both treatment naïve participants and participants on stable nucleos(t)ide therapy. Both groups of study participants experienced declines in HBsAg, including some achieving HBsAg levels <LLOQ, followed by acute ALT elevations (refer to Investigator's Brochure [GSK Document Number 2019N425040_00]).

Although there are some differences in regional treatment guidelines for starting nucleos(t)ide therapy, most indicate the initiation of treatment at the onset of active hepatitis, defined as high levels of HBV DNA and elevated ALT [EASL, 2017; Sarin 2016; Terrault, 2018]. Treatment with nucleos(t)ides is very effective in controlling HBV replication and acute hepatitis over a treatment period of approximately 6 months, resulting in undetectable levels of HBV DNA in the blood and normalisation of ALT. As these patients typically require lifelong therapy with frequent monitoring, they are a common patient subpopulation within speciality hepatology centres and clinics.

Patients whose infection is controlled by nucleos(t)ides still have high levels of HBsAg in serum due to the presence of high levels of HBV cccDNA and integrated DNA in infected hepatocytes. A recently completed GSK-sponsored Phase IIa study (205670) investigated safety, tolerability, pharmacokinetics and pharmacodynamics of a related HBV-targeted

antisense oligonucleotide (ASO), GSK3389404, in nucleos(t)ide-controlled participants with HBeAg-positive and HBeAg-negative CHB. Part 2 of the study enrolled 66 participants (18 HBeAg-positive, 48 HBeAg-negative) in the Asia-Pacific region, including Hong Kong, China, Japan, Philippines, Singapore and South Korea. Mean (SD) baseline serum HBsAg was 2.94 (0.56) $\log_{10}$ IU/ml, with 4/66 participants having baseline serum HBsAg levels above 10,000 IU/ml [GSK Document Number 2020N429086_00].

CHB patients on stable nucleos(t) therapy have been selected for study 212602 as they are considered to have the most favourable benefit:risk profile for early PoM/PoC studies with experimental therapies targeting HBsAg as an endpoint [Lok, 2017].

Selection of HBeAg-negative patients

The utility of serum HBsAg as a predictor of treatment response in CHB has been widely investigated, particularly in those treated with PEG-interferons. Lower serum HBsAg at baseline and rapid early declines on-treatment have both been associated with higher rates of sustained loss of HBsAg and functional cure [Lee, 2018; Liu 2018]. Although the relationship between baseline serum HBsAg and response to GSK3228836 has yet to be established, it is reasonable to assume that participants with lower levels of HBsAg at screening will be more likely to achieve HBsAg levels <LLOQ on treatment. As HBeAg-negative patients typically have lower levels of serum HBsAg than HBeAg-positive patients, the HBeAg-negative population has been selected for study 212602 in order to enrich for potential responders.

Previous GSK clinical experience in CHB supports the observation that serum HBsAg levels are lower in HBeAg-negative patients than HBeAg-positive patients. In study ISIS 505538-CS3, there were a wide range of baseline HBsAg levels reported across all 4 Cohorts (entry criteria for serum HBsAg >50 IU/mL). Final data from that study highlight, as expected, a lower baseline HBsAg level in HBeAg-negative than HBeAg-positive participants. In Cohort 4 of study ISIS 505538-CS3, which included only HBeAg-negative participants on stable nucleos(t)ide therapy (n=7), baseline serum HBsAg levels ranged from 173.7-30,943 IU/mL. Only one participant in Cohort 4 had a baseline serum HBsAg level above 10,000 IU/mL [GSK Document Number 2020N429086_00]. A recently completed GSK-sponsored Phase IIa study (205670) investigated safety, tolerability, pharmacokinetics and pharmacodynamics of a related HBV-targeted ASO, GSK3389404, in nucleos(t)ide-controlled participants with HBeAg-positive and HBeAg-negative CHB. This study recruited 66 participants (18 HBeAg-positive, 48 HBeAg-negative) in the Asia-Pacific region, including Hong Kong, China, Japan, Philippines, Singapore and South Korea. Mean (SD) baseline serum HBsAg was 2.86 (0.51) $\log_{10}$ IU/mL in HBeAg-negative participants compared to 3.04 (0.56) IU/ml in HBeAg-positive participants [GSK Document Number 2020N429086_00].

Rationale for studying 12 weeks of treatment with GSK3228836

The current hypothesis of functional cure is based on the ability of a patient to raise an effective immune response to HBV in infected hepatocytes once immunosuppressive HBsAg has been lost from the blood. The duration of suppression of HBsAg required to enable reconstitution of anti-HBV immunity is still unknown. In study ISIS 505358-CS3 treatment of participants with CHB on stable nucleos(t)ide therapy with 300 mg/week of

GSK3228836 for 4 weeks duration was associated with reductions in HBsAg. Median decline in HBsAg from baseline over 4 weeks was -3.166 IU/ml, with two participants achieving HBsAg levels <LLOQ while on treatment, or shortly after. Both of these participants saw reversable elevations in ALT to >3X ULN after HBsAg had fallen <LLOQ. Of note, in participants that did not become HBsAg <LLOQ, reductions of HBsAg had not yet reached a plateau during treatment, suggesting that continued dosing has the potential to further reduce HBsAg levels. Taken together, the data suggest that a longer duration of treatment with GSK3228836 may be required to increase the rate of participants achieving HBsAg levels <LLOQ. Twelve weeks duration of treatment with 300 mg GSK3228836 has been selected as optimal to assess the primary endpoint of achieving HBsAg < LLOQ in study 212602. Longer durations of treatment (up to 24 weeks) will be explored in other clinical trials during the development of GSK3228836 in order to optimise efficacy in terms of sustained virological response and functional cure.

Rationale for inclusion of fine needle aspirates of the liver

To date, much of what is understood of the virology and immunobiology of CHB infection has come from studies of the peripheral blood compartment of infected patients in observational and a limited number of interventional clinical studies. More recently, a small number of studies using conventional liver biopsy or alternative liver-sampling techniques to study liver resident immune subtypes have revealed substantial differences between the systemic and liver compartments, including defective T-cell-mediated immunity against HBV in the liver of chronically infected patients [Gill, 2019].

Where liver biopsies were once considered routine in the diagnosis and monitoring of liver disease in patients with CHB, they have been mostly replaced by non-invasive tests in recent years, limiting the opportunity to study the liver-resident immune subpopulations in clinical studies. Research papers have recently described the use of fine needle aspirates (FNAs) as a rapid and better-tolerated alternative to conventional core biopsies for sampling intrahepatic immune cells, including T-cells and cells of the innate immune system, such as liver-resident NK cells. This novel technique has been shown to be safe and effective for repeat sampling of the same patient over several weeks/months, permitting longitudinal analysis of immune responses to therapeutic interventions in clinical trials for the first time [Gill, 2019; Tjwa, 2016; Sprengers, 2005].

In study 212602, it is proposed to perform a total of 5 FNAs at preselected timepoints (plus up to 1 optional FNA) during the 45-week study duration (see Section 1.2). The timing of FNAs has been selected to assess intrahepatic immunological changes at different stages of treatment with GSK3228836, and in the follow-up period (Table 6)

Table 6 Timepoints for Fine Needle Aspirates

FNA number	Time point (Study Week)	Description
1	Week -1	Baseline sample
2	Week 3	Early on-treatment. Preceding anticipated marked declines in serum HBsAg level.
3	Week 5	Anticipated start of HBsAg level <LLOQ in responders and start of ALT flare (Based on review of efficacy data in study ISIS 505358-CS3).
4	Week 13	End of treatment
5	Week 36	End of follow-up
6 (Optional)	Any between Week 6 and Week 36	To be determined following discussion between investigator and medical monitor. May be triggered by changes in serum HBsAg levels or ALT.

4.2.1. Participant Input into Design

A small group of patients with CHB were asked to review an example informed consent form in related study 209668. 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. Input from these 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.

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 level <LLOQ that persisted for 102 and 28 days, respectively. In both participants who achieved HBsAg level <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 nucleos(t)ide therapy. Three of five GSK3228836-treated participants (60%) achieved HBsAg reductions >3 $\log_{10}$ 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 participants achieving and sustaining HBsAg levels <LLOQ.

Study 212602 will explore weekly dosing of GSK3228836 300 mg for 12 weeks (with the loading doses) in participants on stable nucleos(t)ide therapy.

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; Baraclude, 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 currently receiving stable nucleos(t)ide analogue therapy, 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 must be adequately suppressed, defined as plasma or serum HBV DNA <90 IU/mL 5. HBeAg-negative 6. Alanine Transaminase (ALT) ≤2 X ULN
SEX
7. 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 included in Appendix 4 of the protocol

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
8. Capable of giving signed informed consent as described in Section 10.1 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:
   - Current or past history of Hepatitis C virus (HCV)
   - Human immunodeficiency virus (HIV)
   - Hepatitis D virus (HDV)
3. History of or suspected liver cirrhosis and/or evidence of cirrhosis as determined by
   - 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
   - Regardless of APRI or Fibrosure/FibroTest score participants will be excluded from the study if their past history includes one of the following criteria:

   i. Liver biopsy showing Metavir 4 or equivalent
   ii. Liver stiffness >12 kPa
4. Diagnosed or suspected hepatocellular carcinoma as evidenced by the following
   - Alpha-fetoprotein concentration ≥200 ng/mL
   - 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 enrolment.
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 by itself won't be an exclusion criterion - but if results are borderline positive or positive:
   - Participants that meet this criteria may be considered for inclusion 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 or baseline AND evidence of past history or current manifestations of vasculitic/inflammatory/auto-immune conditions
   - 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
    - Current alcohol use as judged by investigator to potentially interfere with participant compliance
    - 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 • Serum albumin <3.5 g/dL • Glomerular filtration rate (GFR) <60 mL/min /1.73m^2 as calculated by the CKD-EPI formula. • INR >1.25 • Platelet count <140 X 10^9/L • 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 • 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 enrolled. 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. Criteria for Temporarily Delaying Administration of Study Intervention

See Section 7.1 for guidance on treatment hold and criteria for temporarily delaying GSK3228836.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

CCI

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 labelled 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

This is an open-label study with one treatment arm. Randomization and blinding are not applicable. As the study is unblinded, the risk of potential bias will be mitigated by ensuring that, where feasible, the GSK central team's exposure to virological biomarker results, including HBsAg, HBsAb and HBV DNA, is limited. Details will be included in separate blinding plans.

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. Dose Modification

Dose modifications are not planned for this study.

6.6. Continued Access to Study 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 based on their response.

6.7. 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.

6.8. 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 nucleos(t)ides, 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).

6.8.1. 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 their therapy over the duration of the study.

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

6.8.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications are not permitted during the study:

- PEG-interferon or other immunomodulating therapies
- Immunosuppressing drug (e.g., prednisone) use >2 weeks duration from 3 months prior to Screening through the final Follow-up visit (see Section 5.2), unless required for safety
- Prior treatment with any oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing through the final Follow-up visit

- Creatine-containing gym supplements
- Anti-coagulation therapies (for example warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel). Note: occasional use of aspirin is permitted, please consult the medical monitor if needed.

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. In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. Participants that withdraw from treatment for any reason should be encouraged to complete all their on-treatment and follow-up visits and assessments. Should the participant not wish to continue with weekly visits in the on-treatment window, a reduced visit schedule may be considered. The reduced visit schedule should include Weeks 3, 5 and 12 and all specified assessments as a minimum. 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

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 (i.e., pre-dose) as indicated. The participant must then attend the 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 stopping, and increased monitoring 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.

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

- a participant meets one of the conditions outlined in Table 7.
- 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 7 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 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 7 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	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

ALT = alanine aminotransferase; IMP = investigational medicinal product; ULN = upper limit of normal

*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.

- Any clinically significant deterioration 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 drug-induce liver injury (DILI) or the participant may continue with dosing.

The procedures listed below are to be followed if a participant meets any of the liver chemistry stopping criteria defined in Table 7:

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 case report form (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 Events CRF.

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

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

7.1.2. Drug Induced Vascular Inflammation 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 the lower limit of normal (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 (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 hs-CRP; 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 hs-CRP, MCP-1, Bb, C5a) without clear alternative explanation.
- Discontinue study treatment permanently if suspect clinical sequelae of complement activation, drug induced vascular inflammation, 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 8 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

Participant Level Stopping Criteria

- Hold study treatment in participants who develop ACR ≥0.5 mg/mg (500 mg/g), or eGFR >25% reduction from baseline, 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
- 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
- Delay in treatment of suspected RPGN should be avoided.

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.

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 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. 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 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 Section 1.3). 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 (see Section 1.3).
- 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 measurement for efficacy in this study is the assessment of 12 weeks of GSK3228836 treatment on serum HBsAg levels in participants with CHB. The primary efficacy endpoint is achieving serum HBsAg level <LLOQ by Week 12.

Any HBsAg greater than LLOQ after achieving HBsAg seroclearance 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.

HBsAg and HBV DNA are collected for primary and secondary efficacy endpoints as per the SoA (see Section 1.3). Details of sample collection can be found in the SRM.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3). 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. Symptoms directed exams will be conducted at all other time points (please refer to the SRM for details).

- 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).
- 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 the following in relation to ISRs and ISRs should be recorded as AEs:

- Pain or tenderness
- Erythema or redness
- Induration or swelling
- Pruritus

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 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 (see Section 1.3).

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.

8.2.6. 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).

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

All AEs and SAEs will be collected from the signing of the informed consent form 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 case report form (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.

8.2.6.2. 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.

8.2.6.3. 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.

8.2.6.4. 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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.

8.2.7. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until no longer than 6 to 8 weeks following the estimated delivery date.

If a pregnancy is reported, the investigator 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.

8.2.8. Cardiovascular and Death Events

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

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

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

8.2.9. Adverse Events of Special Interest

8.2.9.1. 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.

8.2.9.2. 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 patients 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

8.2.9.3. 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.

8.2.9.4. 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.

8.2.9.5. 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.

8.3. Pharmacokinetics

Blood samples will be collected for measurement of GSK3228836 trough plasma concentrations and plasma concentrations during the terminal elimination phase as specified in the SoA (see Section 1.3).

- 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.
- PK samples will be used to evaluate the PK of GSK3228836, and explore PK-PD relationships.
- Samples collected for PK analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.4. Biomarkers

CCI [redacted] . CCI [redacted]

CCI [redacted]

CCI [redacted]

8.5. Resistance Monitoring

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 resistance monitoring for participants who experience virological breakthrough whilst still receiving GSK3228836 (i.e., haven't completed treatment).

CCI [redacted]

- [redacted]
- [redacted]

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 with sub-optimal HBsAg levels in the absence of detectable HBV DNA.

8.6. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of the study is to assess the efficacy of 12 weeks of GSK3228836 treatment in Hepatitis B e-antigen negative participants on nucleos(t)ide analogue therapy. The primary endpoint is achieving serum HBsAg level <LLOQ by Week 12 (at any time point up to and including Week 12) without the use of PEG-interferon or other immunomodulator therapies in CHB participants who receive at least one dose of IP.

An estimation approach with no hypothesis testing will be used to address the primary objective. The primary assessment of interest is the point estimate of percent of participants achieving serum HBsAg level <LLOQ (without the use of PEG-interferon or other immunomodulator therapies) by Week 12 with the 95% credible interval. Other intercurrent events such as discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). In addition, posterior probabilities that the true percent is greater than the desired threshold of 50% will be provided using a Bayesian probability approach.

9.2. Sample Size Determination

Approximately 20 participants will be targeted to assign to treatment.

Primary Endpoint

It is assumed that the number of participants achieving serum HBsAg level <LLOQ by Week 12 without the use of PEG-interferon or other immunomodulator therapies follows a Binomial distribution, with a weakly informative prior beta (0.5, 0.5) for the true response. The precision for a range of true response rates with 95% credible intervals are shown in Table 9.

Table 9 95% Credible Interval for Percent of Participants achieving HBsAg <LLOQ by Week 12

Sample size per arm	Number of Participants with HBsAg <LLOQ	Percent of Participants with HBsAg <LLOQ	95% Credible Interval*
20	8	40%	20% – 61%
	10	50%	29% - 71%
	12	60%	39% - 80%
	14	70%	50% - 87%
	16	80%	61% - 94%

*95% highest posterior density interval

With 20 participants, if the observed response rate is 60%, 70% and 80%, then the lower bound of the 95% credible interval excludes values below 39%, 50% and 61%, respectively. The posterior probability that the percent of participants achieving HBsAg<LLOQ by Week 12 is greater than 50% 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 percentage of participants achieving serum HBsAg level <LLOQ exceeds 50% (desired for further mechanistic exploration of the therapeutic effects of GSK3228836 via intrahepatic immunophenotyping) are shown in Table 10, for various assumed sample sizes and true response rates. A weakly informative prior beta (0.5, 0.5) is used. With a sample size of 20 participants, if there are at least 12 participants achieving HBsAg <LLOQ (observed percent of 60%) then the posterior probability that the true percent is greater than 50% will be greater than 75%.

Table 10 Study Operating Characteristics by Sample Size

Criteria	Sample Size	Min N (%) of Participants with HBsAg <LLOQ required for meeting Criteria	Probability of Meeting Criteria if True Response Rate =						
			30%	40%	50%	60%	65%	70%	75%
Probability (true response rate >50%)>75%	10	7 (70%)	1%	5%	17%	38%	51%	65%	78%
	15	9 (60%)	2%	10%	30%	61%	75%	87%	94%
	18	11 (61%)	1%	6%	24%	56%	73%	86%	94%
	20	**12 (60%)**	**1%**	**6%**	**25%**	**60%**	**76%**	**89%**	**96%**
	24	14 (58%)	0%	5%	27%	65%	82%	93%	98%
	30	17 (57%)	0%	5%	29%	71%	87%	96%	99%

* response rate defined as percent of participants achieving HBsAg<LLOQ by Week 12

Based on these operating characteristics, for a true response rate of 60%, the proposed sample-size of 20 has 60% probability of confirming a true rate of at least 50%, and if the true rate is 70%, there is an 89% chance of confirming a true rate greater than 50%.

Biomarker Endpoints

Given a sample size of 20, the confidence intervals for the ratio in change from baseline in RNAseq (signature) scores between those achieving versus not achieving HBsAg<LLOQ are shown below, assuming a range of effect sizes and between-participant coefficients of variation (CVb).

Example of one scenario with 60% of the participants achieving HBsAg < LLOQ is given below. With relatively smaller between participant variability and larger effect size, a sample size of 20 is appropriate to achieve an acceptable level of precision in detecting the differential responses in biomarker outcomes corresponding to HBsAg responses. For

example, in the scenario where 60% of participants achieve HBsAg <LLOQ, if CVb = 0.4, the 95% CI excludes 1 for geometric mean ratios of 0.6 and below, and for 1.7 and above.

12 Participants (60%) Achieving HBsAg<LLOQ)							
CVb	95% CI for Ratio of Geometric Mean of Fold Change from Baseline for Participants achieving vs. not achieving HBsAg<LLOQ						
	0.6	0.8	1	1.2	1.4	1.7	2.0
0.2	**[0.50, 0.73]**	**[0.66, 0.97]**	[0.83, 1.21]	[0.99, 1.45]	**[1.16, 1.69]**	**[1.41, 2.06]**	**[1.65, 2.42]**
0.4	**[0.41, 0.87]**	[0.55, 1.16]	[0.69, 1.45]	[0.83, 1.74]	[0.97, 2.03]	**[1.17, 2.46]**	**[1.38, 2.89]**
0.6	[0.35, 1.02]	[0.47, 1.36]	[0.59, 1.70]	[0.71, 2.04]	[0.82, 2.38]	[1.00, 2.89]	**[1.18, 3.40]**
0.8	[0.31, 1.18]	[0.41, 1.57]	[0.51, 1.96]	[0.61, 2.36]	[0.71, 2.75]	[0.87, 3.34]	**[1.02, 3.93]**
1	[0.27, 1.33]	[0.36, 1.78]	[0.45, 2.22]	[0.54, 2.67]	[0.63, 3.11]	[0.77, 3.78]	[0.90, 4.44]
1.5	[0.21, 1.70]	[0.28, 2.27]	[0.35, 2.83]	[0.42, 3.40]	[0.49, 3.97]	[0.60, 4.81]	[0.71, 5.66]

There are no plans for sample size re-estimation. In certain cases, including but not limited to higher than anticipated drop-out rate, higher than anticipated rates of efficacy, or large variability in ALT flare patterns, the sample size may be increased to no more than 24.

9.3. Analysis Sets

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

Participant Analysis Set	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 participants who received at least one dose of study treatment
Safety	All participants who received at least one dose of study treatment
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 analyzed.

Defined Analysis Data Sets	Description
Analysis set for primary estimand	All Intent to Treat Participants including all observations on and off treatment.
Analysis set for secondary estimands	All Intent to Treat Participants including all observations on and off treatment.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database release. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

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

9.4.2. Primary Endpoint(s)

The primary analysis will be conducted once the last participant has completed the Week 36 visit (completed 24-weeks of follow-up period) and database lock has been

achieved. The primary efficacy endpoint is achieving serum HBsAg level <LLOQ at any time point during 12-weeks (including Week 12) of GSK3228836 treatment.

The Primary Estimand supporting the primary objective of the study is defined as:

- Population: Participants with CHB who receive at least 1 dose of IP
- Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy)
- Variable: Achieving serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies
- Population-level summary: Percent of participants that achieve serum HBsAg level <LLOQ at any time point up to and including Week 12
- Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy).

The primary estimand is the percentage of participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) who achieve serum HBsAg level <LLOQ at any time point up to and including Week 12, without the use of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP or adherence to IP. If PEG-interferon or other immunomodulator therapies are used, then the participant's primary outcome will be treated as a failure.

9.4.3. Primary Analyses

Point estimate of the percentage as well as the 95% credible interval (Highest Density Interval, HDI) of participants achieving serum HBsAg level <LLOQ by Week 12 will be provided.

A Bayesian approach will be used to estimate the posterior probability of participants that achieve serum HBsAg level <LLOQ by week 12 exceeding 50%. A weakly informative prior beta (0.5, 0.5) will be used.

Let Y be the number of responders from N participants,

$Y \sim \text{Binomial}(N, p)$

Where p is virologic response rate.

The posterior distribution for p is

$P(p|y, N) \sim \text{Beta}(y + 0.5, N - y + 0.5)$

The posterior probability that the true rate of participants achieving LLOQ by Week 12 being greater than 50% will be calculated from the posterior distribution.

Additional analyses for the primary endpoint may be included as supportive analyses.

9.4.4. Secondary Endpoint(s)

Estimands supporting the secondary objective of assessing sustainability of serum HBsAg loss by GSK3228836 for up to 24 weeks off-treatment are defined as follows:

- The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies. If PEG-interferon or other immunomodulator therapies are used then the participant's outcome will be treated as a failure.

- Variables:
    - Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies
        - HBsAg from Week 13 to Week 36 will be used to assess sustained HBsAg response after the planned end of GSK3228836 treatment.
    - Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies
        - HBsAg for 24 weeks after end of actual treatment will also be used to assess sustained HBsAg response after the actual end of GSK3228836 treatment.

- Population Summary: percentage of participants for each variable.

- Analysis windows for the post GSK3228836 treatment assessments will be defined in the analysis plan.

Estimands supporting the secondary objective of assessing sustainability of serum HBsAg and HBV DNA (Sustained Virologic Response) loss by GSK3228836 for up to 24 weeks off treatment are defined as follows:

- The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies. If PEG-interferon or other immunomodulator therapies are used then the participant's outcome will be treated as a failure.

- Variables:
    - Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment

        - HBsAg and HBV DNA from Week 13 to Week 36 will be used to assess sustained virologic response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies.
    - Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment
        - HBsAg and HBV DNA for 24 weeks after end of actual treatment will be used to assess sustained virologic response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies.

- Population Summary: percentage of participants for each variable.

- Analysis windows for the post GSK3228836 treatment assessments will be defined in the analysis plan.

Estimands supporting the secondary objective of assessing the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows:

- Population: Participants with CHB who receive at least one dose of IP

- Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy)

- **Intercurrent events**: Discontinuation of, interruption of, adherence to IP will be ignored (treatment policy). PEG-interferon or other immunomodulator therapies will be handled with hypothetical strategy.

1) Categorical Variables:

- Achieving HBsAg <LLOQ over time
- Achieving HBV DNA <LLOQ over time
- Achieving HBsAg <LLOQ and HBV DNA <LLOQ over time
- Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 $\log_{10}$ IU/mL) over time
- *ALT>3X ULN over time*
- Categorical changes from baseline in HBe antibody (anti-HBeAg)
- Additional categories of changes from baseline may be added in the RAP.

- **Population summary:** Percent of participants in each category.

2) Continuous Variables:

- Actual values and change from baseline over time for HBsAg and HBV DNA
- HBs antibody (anti-HBsAg) levels over time
- Area under the curve (AUC) for ALT on treatment (12 weeks), during follow up (24 weeks), and on treatment + follow up (36 weeks).

- **Population summary**: mean values and/or mean changes from baseline for each variable

3) Time to Event Variable

- Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks (treatment + follow up)

- Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN)

Missing data for variables in this group of estimands will be ignored, only available data will be summarized. Outcome will be assumed missing (Missing At Random) from the timepoint when participants first receive PEG-interferon or other immunomodulator therapies.

Further details will be provided in the RAP.

9.4.5. Safety Endpoints

All safety analyses will be based on the Safety Population.

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

The percent of participants reporting adverse events (AEs) will be tabulated. 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 and vital signs (absolute values and change from baseline) will be summarized by visit. In addition, the maximum post-baseline toxicity grade (based on DAIDS categories) will be tabulated.

9.4.6. Exploratory Endpoint(s)

CCI

[redacted]

CCI

9.5. Interim Analysis

Data will be incorporated into regular safety reviews by an IDMC and may be used to supplement the safety data review for the Phase IIb B-Clear study [GSK Document Number 2019N420582_00, Study 209668].

9.6. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will review ongoing safety data in this study as described in Section 9.5. The IDMC will meet on a regular basis as outlined in the charter.

The first data review meeting will be held approximately 18 weeks post first-participant-first-dose (data cut at approximately 12 weeks post-first participant first dose [FPFD]). Thereafter, the frequency of scheduled meetings depends on participant enrolment, information accumulated and safety event rates but will occur approximately every 3 months.

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.

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

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her 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

Independent Data Monitoring Committee: 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 patient 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.

Internal Safety Review Team (SRT): A separate internal safety review team will meet to review all participants' safety data on a regular basis.

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 patient-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 and its origin can be found in the RAP
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

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 11 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 in parallel

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 in parallel.

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 11 Protocol-Required Laboratory Tests

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 Glutamic-Pyruvic Transaminase (SGPT)	Total Protein

Laboratory Assessments	**Parameters**			
	Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• By dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive urine or serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]			
Other Tests	• Follicle-stimulating hormone and estradiol (as needed only) • 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 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, aPTT, Alpha-fetoprotein, ANCA (MPO-ANCA, PR3-ANCA), APRI/Fibrosure, Complement factors C3, C4, C5a, and Bb, hs-CRP, MCP-1, angiopoetin II, PBMC, soluble protein, PAX Gene • Urine ACR • Genetic sample • Viral Sequencing: HBV Genotype, 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 • PBMCs may be processed at the local laboratory as agreed with the Sponsor in advance.			

Additional tests listed under safety follow-up processes	**<u>Liver Chemistry Stopping Criteria[3]</u>**
	• 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
	  o Hepatitis B virus DNA load
	  o Hepatitis C virus RNA load
	  o Hepatitis D virus antibody
	• PK sample
	• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
	• Fractionated 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			

Laboratory Assessments	Parameters
	Drug Induced Vascular Inflammation 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 6. 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: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

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

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

Definition of Unsolicited and Solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

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 intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward

for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorised medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

- Congestive heart failure
- 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 required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess the 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.

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.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

The DAIDS Table [DAIDS, 2017] is used for grading AEs and provided as a guidance for patient management for the consideration of the PI. The DAIDS table will be used to

grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

The DAIDS Table is available at the following link:

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

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) 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 Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the study reference manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Notes:

- 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - 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, gonadal dysgenesis), 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.

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.

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 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.

If criteria for permanent discontinuation of IP are met, 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).
    - 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 Events CRF.

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

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

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. 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: Abbreviations and Trademarks

ACR	albumin to creatinine ratio
AE	adverse event
ALK	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibody
APRI	aspartate aminotransferase-platelet index
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0-24)}$	area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose
$AUC_{(0-\infty)}$	area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BLRM	Bayesian logistic regression model
BMI	body mass index
BMD	bone mineral density
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
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
DILI	drug-induced liver injury
dL	deciliters
DMPK	drug metabolism and pharmacokinetics
DNA	deoxyribonucleic acid
EC_{90}	concentration that produces 90% of maximal effect
EC_{99}	concentration that produces 99% of maximal effect
ECG	electrocardiogram
EPIP	Electronic Protocol Inquiry Platform
ET	early termination
FNA	fine needle aspiration
FPFD	first participant, first dose
FSH	follicle stimulating hormone
GalNAc	N-acetyl galactosamine
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
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
HPF	high-power field
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
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
Lb	pounds
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification
m^2	square meters
MCMC	Markov Chain Monte Carlo
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
Mg	milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
Min	minutes
mL	milliliters
mm^3	cubic millimeters
MOE	methoxyethyl
Msec	milliseconds
MSDS	Material Safety Data Sheet
NA	nucleos(t)ide analog
NCA	non-compartmental analysis
Ng	nanograms
NOAEL	no observed adverse effect level
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
RR_{ACT}	response rate in the active group
RR_{PBO}	Response rate in the placebo group
SAD	single ascending dose

SAE	serious adverse event
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
SoA	schedule of activities
SOP	standard operating procedure
SPEP	serum protein electrophoresis
SRM	Study Reference Manual
SRT	Safety Review Team
$t_{½}$	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
WOCBP	women of childbearing potential

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