TITLE PAGE

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

Protocol Number: 209348/ Amendment 01

Compound Number: GSK3228836

Brief Title: Phase IIb Study of Sequential GSK3228836 and Peginterferon Treatment in Participants with Chronic Hepatitis B (B-Together)

Study Phase: Phase IIB

Acronym: B-Together

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Regulatory Agency Identifying Number(s):

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Medical Monitor Name and Contact Information:

Can be found in the Study Reference Manual (SRM)

SPONSOR SIGNATORY:

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

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Dickens Theodore, MD, MPH Senior Director, Clinical Development Immunology and Fibrosis 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**	**Document Number**
Amendment 01	24-SEP-2021	TMF-13966464
Original Protocol	16-OCT-2020	2020N427224_00

Amendment 01 24-SEP-2021

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

Overall Rationale for the Amendment:

The primary drivers for this amendment were non-substantial changes, mostly for clarification, alignment with Study 209668, and to incorporate recommendations suggested in regulatory feedback.

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

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.3 Schedule of Activities, Table 2, Table 2	Added thyroxine (T4) to thyroid assessments.	Correction.
Section 1.3 Schedule of Activities tables, as required and applicable text throughout	Changed “anti-HBsAb” to “anti-HBsAg” and “anti-HBeAb” to “anti-HBeAg.”	Correction.
Section 1.3 Schedule of Activities, Table 4, Table 5	Removed separate bilirubin assessment as this is included within the chemistry assessments.	Correction.
Section 1.3 Schedule of Activities tables, as required	Specified that hepatitis B virus e-antigen (HBeAg) assessment is only for participants who are HBeAg-positive at Screening.	Correction.

Section # and Name	Description of Change	Brief Rationale
and applicable text throughout		
Section 1.3 Schedule of Activities, Table 7	Added footnote to specify that neuropsychiatric assessments (Columbia Suicide-Severity Rating Scale [C-SSRS] and Beck Depression Inventory-II [BDI-II]) only need to be completed for participants who received at least 1 dose of PegIFN.	Correction.
Section 1.3 Schedule of Activities, Table 7	Added pharmacokinetic (PK) assessment at early termination visit for PegIFN	Correction.
Section 3 Objectives and Estimands and where applicable throughout	Updated text defining the population for the efficacy objectives to align with the definition of intent-to-treat (ITT) population which will be used in efficacy analyses and is defined as all randomized subjects.	To align with Study 209668 (B-Clear).
Section 3 Objectives and Estimands and Section 9.4.3.1 Secondary Estimands	Secondary Efficacy Endpoints: moved HBe antibody (anti-HBeAg) levels from a continuous variable to a categorical variable.	Correction.
Section 5.2 Exclusion Criteria	Medical Conditions Number 3: provide clarity that liver biopsy and stiffness are historical measurements.	Provide clarity to investigators that these are for historical measurements, if available, not to be performed for assessment.
Section 5.3 Inclusion and Exclusion Criteria for PegIFN	Added text to clarify eligibility criteria for patients who meet GSK3228836 liver monitoring hold or stopping criteria to receive treatment with PegIFN.	Clarification requested per the Food and Drug Administration (FDA).
Section 5.3 Table 8 Eligibility Criteria to start PegIFN	Added “vii)” before “Ocular Exam.”	Correction.
Section 6.1 Study Intervention(s) Administered	Changed the address of manufacturer/source of PegIFN (Roche).	Correction.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1 GSK3228836 Liver Chemistry Stopping Criteria	Added text: Cases such as Gilbert syndrome, where baseline bilirubin values are high, should be discussed with the Medical Monitor, to assess if it is a case of drug-induced liver injury (DILI) or the participant may continue with dosing.	To clarify and identify instances where medical monitor should be consulted.
Section 7.1.1 GSK3228836 Liver Chemistry Stopping Criteria	Clarify that the serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) should be conducted if available.	Serum acetaminophen adduct high performance liquid chromatography assay may not be available in all countries.
Section 7.1.2 GSK3228863 Haematological Stopping Criteria	Added text: If the platelet count is uninterpretable or a decreasing trend is noted below lower limit of normal (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.	Clarification and to provide guidance to investigator.
Section 7.1.3 GSK3228836 Drug Induced Kidney Injury (Renal) Stopping Criteria	Updated GSK3228836 drug induced kidney injury (renal) treatment hold/treatment discontinuation criteria to identify changes in albumin to creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) relative to the pre-dose range instead of baseline.	Clarification and to provide guidance to investigator.
Section 8.2.7.1 Columbia Suicide Severity Rating Scale (C-SSRS)	Removed timeframe from C-SSRS screening questions.	Correction.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim Analysis	Removed interim analysis 1.	Interim analysis 1 was originally planned to determine futility and stop enrolment in the study. At the time of this protocol amendment, it was no longer applicable because complete enrolment had already occurred.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 17	Changed SAE reporting bilirubin ≤2X the upper limit of normal (ULN) to >2X ULN.	Correction, due to typo.
Section 10.3.5 Reporting of SAE to GSK	Removed bullet that stated the investigator must show evidence within the electronic case report form (eCRF) of review and verification of the relationship of each serious adverse event (SAE) to investigational product (IP)/study participation (causality) within 72 hours of SAE entry into the eCRF.	To align with updated protocol template.
Throughout	Minor editorial and document formatting revisions	Minor; therefore have not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Brief Title: Phase IIb Study of Sequential GSK3228836 and Peginterferon Treatment in Participants with Chronic Hepatitis B (B-Together)

Rationale:

Study 209348 is intended to evaluate whether up to 24 weeks of treatment with GSK3228836 followed by up to 24 weeks of pegylated interferon (PegIFN) can increase the rate of hepatitis B virus surface antigen (HBsAg) loss in participants on stable nucleos(t)ide analogue (NA) therapy, and whether virologic response can be sustained once PegIFN treatment is discontinued. Efficacy of sequential therapy with GSK3228836 and PegIFN will be compared to treatment with GSK3228836 alone, which is being currently being explored in a separate Phase IIb study, 209668. Study 209348 will also evaluate the safety and tolerability of the treatment regimen.

Key Objectives and Estimands:

Objectives	Estimands
Primary	
Efficacy: To investigate the efficacy of two different durations of GSK3228836 followed by up to 24 weeks of PegIFN therapy in participants with CHB on stable NA therapy.	The main Estimand supporting the primary objective is defined as: • Population: Participants with CHB on stable NA therapy • Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy • Variable (Categorical): Participants achieving Sustained Virologic Response (SVR) (HBsAg <lower limit of quantification (LLOQ) and Hepatitis-B virus deoxy-ribonucleic acid (HBV DNA) <LLOQ) for 24 weeks after the planned end of sequential treatment, without use of any rescue medication • Intercurrent Events: o Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN not related to any wide disruptive events (such as COVID-19 pandemic) will be ignored (treatment policy strategy). o Ineligibility to receive PegIFN will be ignored (treatment policy strategy) o Use of rescue medication (composite strategy). o Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of,

Objectives	Estimands
	interruption in, and non-adherence to GSK3228836 and PegIFN will be handled assuming they had not happened (hypothetical strategy). • Population Summary: The percentage of participants in each treatment group who achieve SVR, without use of any rescue medication The main primary estimand supporting the primary objective in participants with chronic hepatitis B (CHB) on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. Three supplementary Estimands are defined to support the primary objective: • The first supplementary Estimand is defined in the same way as the main Estimand, except the assessment time frame for patients achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. • The second supplementary Estimand is to understand the relationship between the PegIFN duration and achieving SVR for 24 weeks after the actual end of treatment, defined as: o Population: Participants with CHB on stable NA therapy o Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by 24 weeks of PegIFN therapy while on stable NA therapy o Variable: The relationship between SVR for 24 weeks after actual end of treatment and the duration of PegIFN received by participants o Intercurrent Events:

Objectives	Estimands
	▪ Discontinuation and delayed start of, PegIFN, will be accounted to reflect the actual duration from the first to the last dose of PegIFN received (while-on-treatment strategy). ▪ Interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy) ▪ Discontinuation of, interruption in and non-adherence to GSK3228836 will be ignored (treatment policy strategy) ▪ Use of rescue medication (composite strategy). ▪ Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation and delayed start of, PegIFN will be handled with while-on-treatment strategy; wide disruptive events leading to interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy); wide disruptive events leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be ignored (treatment policy strategy). o Population Summary: The percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm The second supplementary Estimand (supporting the primary objective in participants with CHB on stable NA therapy) is the percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm, taking into account discontinuation and delayed start of PegIFN, regardless of interruption in and other non-adherence to PegIFN, regardless of discontinuation of, interruption in and non-adherence to GSK3228836. • The third supplementary Estimand is defined in the same way as the main Estimand, except the strategy for intercurrent events of PegIFN ineligibility for more than 12 weeks and/or missing more than 12 doses of PegIFN will be principal stratum. This supplementary Estimand supporting the primary objective is the percentage of participants in each treatment arm that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in participants

Objectives	Estimands
	with CHB on stable NA therapy and receiving at least 12 doses of PegIFN, in the absence of rescue medication, regardless of discontinuation of, interruptions in or non-adherence to GSK3228836 had they not been affected by wide disruptive events.
Secondary	
Efficacy: To assess the efficacy of GSK3228836 and PegIFN therapy on biomarkers and virus specific antibody responses	The Estimand supporting the objective is defined as: • Population: Participants with CHB on stable NA therapy; For the time to alanine aminotransferase (ALT) normalisation variable, population will be aforementioned participants with baseline ALT >upper limit normal (ULN). • Treatment: 300 mg GSK3228836 for 12, or 24 weeks followed by 24 weeks of PegIFN therapy while on stable NA therapy • Categorical Variables: o Achieving HBsAg <LLOQ and HBV DNA <LLOQ at two time points: (1) the planned end of treatment and (2) at the end of 24 weeks follow-up o Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL) at each scheduled visit or analysis window. o ALT normalisation (ALT ≤ULN) over time in absence of rescue medication in participants with baseline ALT >ULN Population summary is the percentage of participants in each category for each treatment group. o HBe antibody (anti-HBeAg) levels. • Continuous Variables: o Actual values and change from baseline over time for HBsAg, HBV DNA and hepatitis B virus e-antigen (HBeAg) o Actual values and change from baseline over time for HBs antibody (anti-HBsAg) levels over time o Actual values and change from baseline over time for ALT Population summary is the mean values and the mean changes from baseline of each

Objectives	Estimands
	variable for participants in each treatment group. • Time to Event Variable: o Time to ALT normalisation in absence of rescue medication in participants with baseline ALT>ULN Population summary is the Turnbull's estimator for non-parametric estimation of Time to ALT normalisation in each treatment arm • Intercurrent Events: Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be ignored (treatment policy); PegIFN ineligibility will be ignored (treatment policy); Rescue medication will be ignored (treatment policy), except for ALT normalisation which can only be achieved in the absence of rescue medication; Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled with Treatment Policy Strategy. • The group of estimands supporting this objective is the population summary for each variable in each treatment arm in the population regardless of discontinuation of, interruption in or non-adherence to GSK3228836 and PegIFN, and regardless of rescue medication (except for ALT normalisation which can only be achieved in the absence of rescue medication) or PegIFN ineligibility.
Efficacy: To investigate the durability of virologic response after sequential therapy with 12 weeks of GSK3228836 followed by 24 weeks of PegIFN in participants with CHB on stable NA therapy for up to 36 weeks off treatment	The same definition as the above secondary estimand, focusing on the timepoints following the 24 weeks off-treatment period in the treatment arm of 300 mg GSK3228836 for 12 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
Efficacy: To compare efficacy between different treatment durations: 12 or 24 weeks of GSK3228836 followed by 24 weeks PegIFN	The same definition as the primary estimand except treatments and population summary are defined as: • Treatments: Arms 1 and 2. One treatment comparison between Arms 1 & 2 up to 24 weeks off-treatment • Population summary: difference in proportion of participants who achieve SVR between treatment arms The group of estimands supporting this objective in participants with CHB on stable NA therapy is the difference between treatment arms 1 and 2 in the proportion of participants that achieve SVR for 24 weeks after the planned end of sequential treatment, in the absence of rescue medication, regardless of ineligibility to receive PegIFN, regardless of discontinuation of,

Objectives	Estimands
	interruption in or non-adherence to GSK3228836 and PegIFN had they not been affected by wide disruptive events.

Overall Design:

This is a Phase IIb, multi-centre, randomised, open-label study to assess the efficacy and safety of sequential treatment with GSK3228836 (300 mg/week for 12 or 24 weeks) followed by PegIFN (180 mcg/week for up to 24 weeks) in participants with CHB on stable NA therapy. During the GSK3228836 treatment period a 300 mg loading dose will be administered on Day 4 and Day 11. Participants will continue their NA therapy for the duration of the study.

Brief Summary:

The purpose of this study is to investigate the efficacy of 12 or 24 weeks of GSK3228836 followed by up to 24 weeks of PegIFN therapy in participants with CHB on stable NA therapy. Study details include:

Study Duration: 79 weeks

Treatment Duration: 12 or 24 weeks of GSK3228836 followed by up to 24 weeks of PegIFN

Post-treatment Follow-up: 36 or 24 weeks off treatment follow-up (note NA-therapy will continue throughout study)

Number of Participants:

This study will enrol approximately 100 participants. Enrolment, in this case, refers to participants who have passed the screening requirements and entered the study. The expected screen failure rate for participants is 20%.

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

The study team may enrol additional participants to within 10% of the planned 100.

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

Intervention Arms and Duration:

The total duration of the study, including screening, treatment, and post-treatment follow-up, is not expected to exceed 79 weeks for each participant:

- Arm 1: 24 weeks GSK3228836 + 24 weeks PegIFN + 24 weeks off-treatment
- Arm 2: 12 weeks GSK3228836 + 24 weeks PegIFN + 36 weeks off-treatment

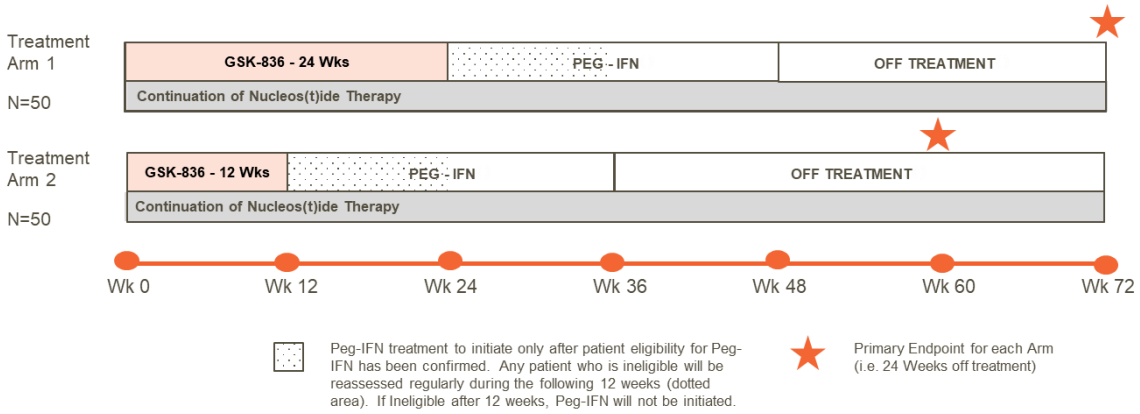
A 45-day screening window is included in the total study duration. Eligible participants who fall outside of the 45-day window may be re-screened at the discretion of the Investigator/site.

There are no plans for group dose adjustments. Individual dose adjustments for GSK3228836 for safety are outlined in the monitoring/stopping criteria. Individual dose adjustments for PegIFN for safety are outlined in the monitoring/stopping criteria and are permitted down to 90 mcg/mL.

Participants that leave the study early will not be replaced.

Data Monitoring/ Other Committee: Yes

1.2. Schema



1.3. Schedule of Activities (SoA)

Both treatment arms will use the same Screening Table (Table 1). Separate tables have been produced for the GSK3228836 treatment period (Table 2 and Table 3). Both treatment arms will use the same PegIFN Treatment Table (Table 4), Reassessment of PegIFN Eligibility Tables (Table 5 and Table 6; only required if participant is ineligible to start PegIFN as per Table 4) and Off Treatment Follow-up Table (Table 7).

[China specific Schedule of Activities can be found in Appendix 7: Country-specific requirements]

Instructions that are applicable to all treatment arms include:

- In selected countries/sites, participants will have the option to use a centralised home nursing provider. Only selected visits will have the option to be performed as a home visit, these will include drug administration, blood draws, participant assessments and data collection. The full specifications of the home nursing services will be outlined in the Study Reference Manual (SRM).
- Haematology (platelet count) will be analysed at a local laboratory prior to each GSK3228836 dose. The blood draw can be taken the day before GSK3228836 dosing. Results must be available prior to dosing. Haematology samples will be collected for central laboratory assessments in parallel. After GSK3228836 treatment is completed, haematology is only collected centrally on weeks of clinic visits.
- If a participant is not eligible to start PegIFN, eligibility will be reassessed. If the participant does not become eligible after 13 weeks, PegIFN will not be initiated in order to ensure participants receive at least 12 weeks of PegIFN treatment. Irrespective of the week that a participant starts PegIFN, the final dose will be given on Study Week 48 for Arm 1 and Week 36 for Arm 2 (Figure 1).
- PegIFN dosing maybe self-administered at home, where local regulations allow at the visits indicated in the SoA (Table 4).

Figure 1 Schematic of Planned GSK3228836 and PegIFN Dosing Periods and Off Treatment Follow-up Period

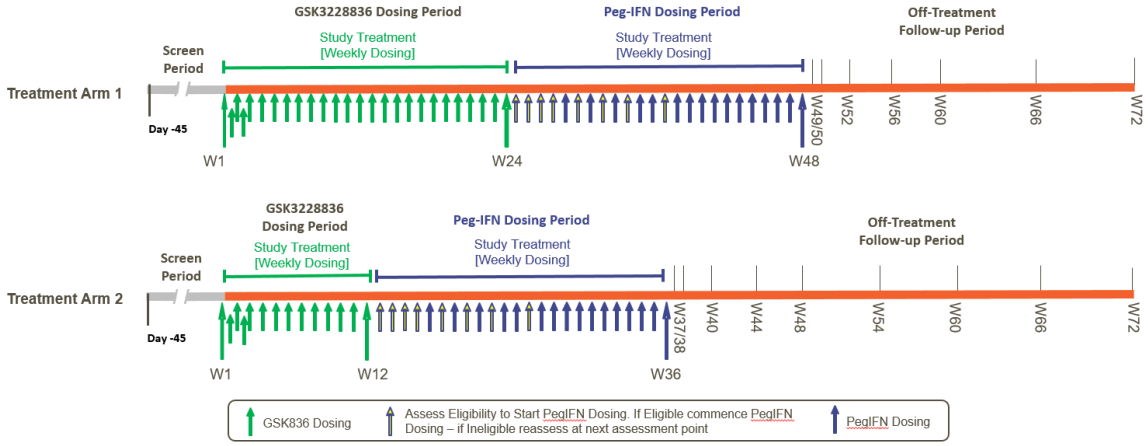


Table 1 Screening (All Treatment Arms)

ASSESSMENTS	
Informed Consent (obtained any time prior to screening)	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
Ocular exam (unless completed within 3 months)	X
12-lead ECG	X
Neuropsychiatric assessment (C-SSRS and BDI-II)	X
LABORATORY ASSESSMENTS	
Serum hCG pregnancy test (women of childbearing potential [WOCBP])	X
FSH/Estradiol (to confirm status of women of non-child-bearing potential)[1]	X
Haematology/Chemistry/Urinalysis	X
TSH, T4	X
Urine ACR	X
PT, INR, aPTT	X
HIV, hepatitis D, and hepatitis C screen	X
Hepatitis B profile (HBsAg, HBV DNA, HBeAg)	X
Alpha-fetoprotein	X
APRI/ FibroSure	X
ANCA (with MPO-ANCA, PR3-ANCA if results are positive or border-line positive)	X
Complement C3, C4, C5a, hsCRP, MCP-1, complement Bb, Ang-2	X

1. As appropriate to confirm menopause

Table 2 GSK3228836 Treatment Period: Treatment Arm 1 (Week 1-24)

Day	1	4	8	11	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162
Week	1	1	2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Window (days)		±1 day			±2	±3 days																				
Randomisation	X																									
GSK3228836 dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																										
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conmed review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom directed exam	X						X				X				X				X				X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG																									X[4]	X[4]
Injection site reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																										
Pregnancy test (WOCBP)	X[1]						X				X				X				X				X			
Haematology [includes platelet and WBC with differential]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, aPTT	X						X				X				X				X				X			X
TSH, T4																										X
Chemistry	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR	X				X		X		X		X		X		X		X		X		X		X		X	X
HBsAg and HBV DNA	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti- HBsAg and anti-HBeAg	X						X				X				X				X				X			
HBeAg[3]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complement C3, C4, C5a, Bb, hs-CRP, MCP-1	X				X		X		X		X		X		X		X		X		X		X		X	
ANCA, Ang II	X						X				X				X				X				X			
PK GSK3228836	X	X	X	X				X						X						X						X
HBV RNA, and Sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)	X				X		X		X		X		X		X		X		X		X		X		X	

Day	1	4	8	11	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162
Week	1	1	2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Window (days)		±1 day			±2	±3 days																				
HBcrAg	X						X						X						X						X	
PBMC Collection for immunophenotyping[2]	X						X							X												
Soluble Protein (immunology)	X				X		X			X				X				X				X				X
PAXGene RNA for expression analysis in whole blood	X						X							X												
OPTIONAL: Genetics	X																									
Archived Samples [serum; plasma]	X				X		X		X		X		X		X		X		X		X		X		X	

1. A WOCBP must have both a confirmed menstrual period prior to the first dose of study intervention AND a negative highly sensitive pregnancy test [urine or serum] within 24 hours before the first dose of study treatment (performed locally)
2. Only for selected sites able to transport to the analysis lab as specified in the SRM
3. Only for participants HBeAg positive at screening
4. ECG to be conducted once at any point from Week 23 and prior to initiation of PegIFN

Table 3 GSK3228836 Treatment Period: Treatment Arm 2 (Week 1-12)

Day	1	4	8	11	15	22	29	36	43	50	57	64	71	78
Week	1	1	2	2	3	4	5	6	7	8	9	10	11	12
Window (days)	±1 day				±2	±3 days								
Randomisation	X													
GSK3228836 dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments														
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant med review	X	X	X	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	X	X	X
12 lead ECG													X[3]	X[3]
Injection site reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
Pregnancy test (WOCBP)	X[1]						X				X			
Haematology [includes platelet and WBC with differential]	X		X		X	X	X	X	X	X	X	X	X	X
TSH, T4														X
PT, INR, aPTT	X						X				X			X
Chemistry	X		X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X	X	X	X	X	X	X	X	X	X
Urine ACR	X				X		X		X		X		X	X
HBsAg and HBV DNA	X		X		X	X	X	X	X	X	X	X	X	X
Anti- HBsAg and anti-HBeAg	X						X				X			
HBeAg (for participants HBeAg positive at screening)	X		X		X	X	X	X	X	X	X	X	X	X
Complement C3, C4, C5a, Bb, hs-CRP, MCP-1	X				X		X		X		X		X	
ANCA, Ang II	X						X				X			
PK GSK3228836	X	X	X	X				X						X
HBV RNA, and sequencing (HBV genotype/phenotype, HBV DNA, and/or RNA)	X				X		X		X		X		X	
HBcrAg	X						X						X	
PBMC Collection for immunophenotyping[2]	X						X							X
Soluble Protein (immunology)	X				X		X			X				X
PAXGene RNA for expression analysis in whole blood	X						X							X
OPTIONAL: Genetics	X													

Day	1	4	8	11	15	22	29	36	43	50	57	64	71	78
Week	1	1	2	2	3	4	5	6	7	8	9	10	11	12
Window (days)	±1 day				±2	±3 days								
Archived Samples [serum; plasma]	X				X		X		X		X		X	

1. A WOCBP must have both a confirmed menstrual period prior to the first dose of study intervention AND a negative highly sensitive pregnancy test [urine or serum] within 24 hours before the first dose of study treatment (locally performed)
2. Only for selected sites able to transport to the analysis lab as specified in the SRM
3. ECG to be conducted at any point from Week 11 and prior to initiation of PegIFN

Table 4 PegIFN Treatment Period

Participants will be assessed using Column 1 below to determine eligibility to begin treatment with PegIFN and moved to the "Yes" column based on the eligibility criteria outlined in Section 5.3. If a participant is determined to be **eligible** for PegIFN dosing, they will begin PegIFN Dosing on Week 1. If a participant is determined to be **ineligible** for PegIFN, see Table 5.

PegIFN Dosing Week	1[a]		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Window	±3 days																								
Confirmed Eligibility for Peg-IFN	Confirm PegIFN Eligibility[1]	Yes[2]																							
Clinic visit[3]	X		X	X	X		X		X		X			X			X				X				X
Peg-IFN dosing		X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X[3]	X	X[3]	X[3]	X[3]	X
Safety Assessments																									
AE/SAE review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptoms directed exam	X				X				X					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				X
Neuropsychiatric assessment (C-SSRS and BDI-II)	X		X	X	X		X		X		X			X			X				X				X
Laboratory Assessments																									
Pregnancy test (WOCBP)		X			X				X		X			X			X				X				X
Haematology [includes platelet and WBC with differential][4]		X	X	X	X		X		X		X			X			X				X				X
TSH, T4							X							X											X
PT, INR, aPTT		X			X									X			X				X				X
Chemistry		X	X	X	X		X		X		X			X			X				X				X
Urinalysis		X	X		X				X					X			X				X				X
Urine ACR		X	X		X				X					X			X				X				X
HBsAg and HBV DNA		X	X	X	X		X		X		X			X			X				X				X
Anti-HBsAg and anti-HBeAg		X			X				X					X			X				X				X
HBeAg (for participants HBeAg positive at screening)		X	X	X	X		X		X		X			X			X				X				X

PegIFN Dosing Week	1[a]		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Window	±3 days																								
Complement C3, C4, C5a, Bb, hs-CRP, MCP-1			X		X				X					X			X				X				
ANCA, Ang II		X			X				X					X			X				X				
PK – PegIFN		X	X		X		X							X			X				X				
PK –GSK3228836		X		X			X				X			X											
HBV RNA, and sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)		X	X		X		X		X		X			X			X				X				X
HBcrAg		X			X				X					X							X				
PBMC Collection for immunophenotyping[5]		X			X									X											
Soluble Protein (immunology)		X	X		X		X							X			X				X				
PAXGene RNA for expression analysis in whole blood		X			X									X											
Archived Samples [serum; plasma]		X	X	X	X		X		X		X			X			X				X				X

a. The first planned PegIFN visit occurs 7 days after the planned GSK3228836 dosing period.

1. Assessment of PegIFN eligibility should be based upon pre-dose safety assessments and laboratory assessments from previous visit
2. For specific Peg-IFN eligibility criteria please refer to protocol Section 4.1; **If ineligible for PegIFN refer to** Table 5.
3. If consistent with local regulations, participants are permitted to self-administer PegIFN at home, site staff may call to assess the participant by phone at this visit and no clinic visit is required. If local regulations or practices prefer to administer PegIFN within the clinic, this can be a clinic visit.
4. Participants in Japan are expected to return for a mid-week haematology assessment during Week 1 and at Week 5 and 7 in accordance with local regulations
5. Only for selected sites able to transport to the analysis lab as specified in the SRM

Table 5 Reassessment of PegIFN Eligibility

If a participant is ineligible for PegIFN dosing immediately (Week 1, Table 4), complete the SoA of PegIFN Eligibility Week 1, Table 5.

Eligibility for PegIFN will be reassessed following the SoA in Table 5 on PegIFN Eligibility Week 2, 3, 4, 6, 8, 10 and 13.

If a participant becomes eligible for PegIFN during any of the reassessment visits, the SoA in Table 4 should be followed starting at the Week 1 "Yes" column for the remainder of PegIFN dosing visits and stopping at the visit number where the combined PegIFN dosing and PegIFN eligibility visits equal "25" – for example, if a participant becomes eligible for PegIFN on PegIFN Eligibility Week 4, the SoA in Table 4 should be followed from Week 1 to Week 21 (Table 6).

PegIFN Eligibility Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Window	±3 days																							
Eligible for PegIFN (Section 4.1)	No	No	No	No		No		No		No			No											
Clinic visit	X	X	X	X		X		X		X			X			X				X				X
Safety Assessments																								
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptoms directed exam		X	X	X		X		X		X			X			X				X				
Vital signs		X	X	X		X		X		X			X			X				X				X
Neuropsychiatric assessment (C-SSRS and BDI-II)		X	X	X		X		X		X			X											
Laboratory Assessments (If not Eligible to begin PegIFN treatment)																								
Pregnancy test (WOCBP)	X			X				X		X			X			X				X				X
Haematology [includes platelet and WBC with differential]	X	X	X	X		X		X		X			X			X				X				X
TSH, T4						X							X											X
PT, INR, aPTT	X			X									X			X				X				X
Chemistry	X	X	X	X		X		X		X			X			X				X				X
Urinalysis	X	X		X				X					X			X				X				X
Urine ACR	X	X		X				X					X			X				X				X
HBsAg and HBV DNA	X	X	X	X		X		X		X			X			X				X				X

PegIFN Eligibility Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Window	±3 days																							
Anti- HBsAg and anti-HBeAg	X			X				X					X			X				X				X
HBeAg (for participants HBeAg positive at screening)	X	X	X	X		X		X		X			X			X				X				X
Complement C3, C4, C5a, Bb, hs-CRP, MCP-1		X		X				X					X			X				X				
ANCA, Ang II	X			X				X					X			X				X				
PK – GSK3228836	X		X			X				X			X											
HBV RNA and sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)	X	X		X		X		X		X			X			X				X				X
HBcrAg	X			X				X					X							X				
PBMC Collection for immunophenotyping[1]													X											
Soluble Protein (immunology)													X											
PAXGene RNA for expression analysis in whole blood													X											
Archived Samples [serum; plasma]	X	X	X	X		X		X		X			X			X				X				X

1. Only for selected sites able to transport to the analysis lab as specified in the SRM

Table 6 PegIFN Dosing for Participants becoming Eligible for PegIFN after Week 1

Become Eligible for PegIFN at PegIFN Eligibility Week (Table 5)	PegIFN Dosing (Table 4) should continue until PegIFN Dosing Week
2	23
3	22
4	21
6	19
8	17
10	15
13	12

Table 7 Off-Treatment Week (OTW) Follow-up: Week 1-24 (Treatment Arm 1) or Week 1-36 (Treatment Arm 2)

Assessments	OTW1[a]	OTW2	OTW4	OTW8	OTW12	OTW18	OTW24	OTW30[1]	OTW36[1]	Early Termination
Window	±3 days									NA
Safety Assessments										
AE/SAE review	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Symptoms directed exam	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric assessment (C-SSRS and BDI-II)[2]	X		X	X	X		X			X
Laboratory Assessments										
Pregnancy test (WOCBP)	X		X	X	X	X	X	X	X	X
Haematology [includes platelet and WBC with differential]	X		X		X		X			X
PT, INR, aPTT	X		X		X		X			X
Chemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis	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	X
Anti-HBsAg and anti-HBeAg	X		X	X	X	X	X	X	X	X
HBeAg (for participants HBeAg positive at screening)	X	X	X	X	X	X	X	X	X	X
Complement C3, C4, C5a, Bb, hs-CRP, MCP-1, ANCA, Ang II	X				X		X			X
PK for PegIFN[2]	X	X	X	X						X
HBV RNA and sequencing (HBV genotype/phenotype; HBV DNA and/or RNA)	X	X	X	X	X	X	X	X	X	X
HBcrAg	X		X	X	X		X			X
PBMC Collection for immunophenotyping[3]	X						X			X
PAXGene RNA for expression analysis in whole blood	X				X		X			X
Soluble Protein (immunology)	X		X		X		X			X
Archived Samples [serum; plasma]	X	X	X	X	X	X	X	X	X	X

a. The first planned Off treatment visit occurs 7 days after the planned PegIFN dosing period.
1. Only applicable for Treatment Arm 2
2. Only for participants that received at least 1 dose of PegIFN.
3. Only for selected sites able to transport to the analysis lab as specified in the SRM.

2. INTRODUCTION

2.1. Study Rationale

Chronic hepatitis B (CHB) infection results in progressive liver disease that may lead to complications such as cirrhosis, liver failure, and hepatocellular carcinoma. 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 hepatitis B virus (HBV) replication in both hepatitis B virus e-antigen (HBeAg)-positive and HBeAg-negative CHB, patients frequently relapse after treatment is discontinued, particularly if hepatitis B virus surface antigen (HBsAg) loss was not achieved. 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.

Recently, a functional cure of CHB infection has been endorsed as an endpoint for new HBV therapies. Functional cure of CHB infection is defined as sustained loss of HBsAg from serum (with or without anti-HBsAg seroconversion) and undetectable HBV DNA in serum, after completion of a finite course of treatment [Lok, 2017; Cornberg, 2019]. Functional cure occurs in only a very small percentage of patients on NA therapy alone (approx. 3% per annum) [Lok, 2017].

Interferons (IFNs) are a group of immunomodulatory drugs approved as a monotherapy for the treatment of certain patients with CHB. Peginterferons (PegIFN) are indicated for the treatment of adult patients with HBeAg positive and HBeAg negative CHB who have compensated liver disease and evidence of viral replication and liver inflammation. Weekly injections of PegIFN for 48 weeks has been demonstrated to achieve functional cure in a small proportion (up to 9%) of CHB patients as monotherapy, or in combination with nucleosides (off-label) [Marcellin, 2016]. Patients that have lower levels of serum HBsAg before starting treatment with PegIFN have been shown to respond better than those with higher levels in clinical trials [Ren, 2019; Lee, 2018].

GSK3228836 is being developed for the treatment of CHB and is a 2'-O-(2-methoxyethyl)-modified chimeric phosphorothioate antisense oligonucleotide (2'-MOE chimeric ASO) drug targeted to HBV ribonucleic acid (RNA). GSK3228836 is complementary to sequences present in all HBV-derived RNA transcripts and its hybridisation to the cognate RNA results in ribonuclease H-mediated degradation. It is highly specific for HBV RNA transcripts and is not homologous to any regions of the human transcriptome, including either a single nucleotide mismatch or with 17 or more consecutive nucleotide matches. GSK3228836 is an antisense oligonucleotide that is designed to inhibit the synthesis of viral proteins (e.g., HBsAg, HBeAg) by targeting HBV RNA without having a direct effect on HBV covalently closed circular DNA (HBV cccDNA) or integrated HBV DNA. Treatment of patients with CHB with GSK3228836 will permit examination of whether reduction of viral proteins allows resumption of a host immune response against HBV virus and infected cells and if longer treatment with GSK3228836 will result in HBsAg loss leading to sustained suppression of HBV replication after cessation of all treatments for CHB.

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 NA therapy. Both groups of study participants experienced declines in HBsAg, including some achieving HBsAg levels < lower limit of quantification (LLOQ), followed by acute ALT elevations (refer to Investigator's Brochure [GSK Document Number 2019N425040_00]).

The efficacy and safety of GSK3228836 treatment for up to 24 weeks duration is currently being evaluated in a Phase IIb study (Study 209668, NCT04449029). It is hypothesised that additional immunomodulatory therapy (such as PegIFN) may be needed to achieve optimal durable HBsAg loss. Study 209348 is intended to evaluate whether up to 24 weeks of treatment with GSK3228836 followed by 24 weeks of PegIFN can increase the rate of HBsAg loss in participants on stable NA therapy, and whether virologic response can be sustained once PegIFN treatment is discontinued. Efficacy of sequential therapy with GSK3228836 and PegIFN will be compared to the response observed with GSK3228836 in the absence of PegIFN in the Phase IIb study, 209668. Study 209348 will also evaluate the safety and tolerability of the treatment regimen.

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 NA therapy. 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. PegIFNs are also approved for treatment of CHB [Lok, 2009; EASL, 2012] and are dosed for a finite treatment duration (usually up to 48 weeks). Because of the frequent and sometimes severe side effects associated with PegIFN and high cost versus a small gain in treatment response, PegIFNs are less frequently used than NAs. Unfortunately, with both the NAs and PegIFN, HBsAg loss and the subsequent development of antibodies to HBsAg are rarely achieved. Rates of HBsAg loss following 12 months of treatment with either a NA and/or PegIFN generally range from 0 to 3% in most studies [Lok, 2009; EASL, 2012], with occasional studies reporting higher rates for example ~10% functional cure after TDF+PegIFN for 48 weeks (off-label) [Marcellin,

2016]. 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 cccDNA or integrated HBV DNA. GSK3228836 directly targets all HBV messenger RNA (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 minimise risk of proinflammatory response associated as a class effect by methylating every cytosine in the antisense oligonucleotide (ASO) sequence as well as avoiding the presence of CpG motifs that can be recognised 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 (AEs) of GSK3228836 may be found in the Investigator's Brochure. Pegylated interferon (Pegasys) was approved by the Food and Drug Administration (FDA) for treatment of HBV in 2005. The safety profile of PegIFN is well characterised. More detailed information about the benefit risk profile of PegIFN can be found in the prescribing information [Pegasys PI, 2017].

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

Currently, there is no evidence that patients with chronic HBV have increased susceptibility to severe acute respiratory syndrome coronavirus-2 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 hospitalised 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.

2.3.1. Risk Assessment

Risks are summarised in the table below. Additional withdrawal/stopping criteria for liver chemistry, drug induced vascular inflammation (DIVI), haematology, renal function, and PK are discussed in Section 7.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3228836]		
Nonclinical Risks: Drug Induced Vascular Inflammation and Complement Activation	Inflammatory and immune changes are recognised 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 7.1.4)
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. Alanine aminotransferase (ALT) elevations (defined as ALT ≥2X upper limit normal (ULN)) were observed in the ISIS 505358-CS3 study. Reductions in HBsAg were temporally associated with ALT elevation in all 11 participants with ALT elevations. HBsAg reduction either preceded the ALT elevations or took place concomitantly with ALT flares. There were no changes in bilirubin.	**Laboratory Evaluations:** hepatic enzyme monitoring as presented in Table 9 **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 7.1.2
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, estimated glomerular filtration rate (eGFR), urinalysis with microscopy and albumin to creatinine ratio (ACR) assessed per the SoA tables **Stopping Criteria:** Monitoring Schedule and Stopping Rules are presented in Section 7.1.3
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 adverse events (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 minimise 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.
Investigational Product (IP) [PegIFN]		
Clinical Risks[1]:		
ALT Flares	Chronic hepatitis B participants experienced transient acute exacerbations (flares) of hepatitis B (ALT elevation greater than 10-fold higher than the upper limit of normal) during PegIFN treatment (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg positive participants, respectively.	**Laboratory Evaluations:** hepatic enzyme monitoring as presented in the SoA **Stopping Criteria:** ALT flares are expected in the study population. Monitoring, dose adjustment and stopping criteria are based on the Pegasys label and presented in Section 7.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide	Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIFN therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other central nervous system (CNS) effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons.	The Columbia Suicide Severity Rating Scale and Beck Depression Inventory-II will be completed by participants as per the SOA during and post treatment. Participants displaying evidence of depression will be managed as per Table 12. If participants develop new or worsening psychiatric symptoms or if suicidal ideation is identified, treatment should be discontinued, and the patient followed up with psychiatric intervention as appropriate. Refer to Section 8.2.7 Suicidal Ideation and Behaviour Risk Monitoring
Decrease in haemoglobin, platelet count, total white blood cell (WBC) count and ANC	PegIFN treatment has been associated with decreases in haemoglobin, platelet count, total WBC count and ANC.	Eligibility for PegIFN treatment will be assessed prior to starting treatment as per Section 5.3 **Laboratory Evaluations:** Haematology monitoring as per the SOA. **Stopping Criteria** Dose adjustment and stopping criteria are based on the Pegasys label and presented in Section 7.2
Endocrine disorders: Thyroid function abnormalities or worsening of pre-existing thyroid disorders	Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alfa interferons, including PegIFN.	Participants with uncontrolled thyroid function are excluded from this study. Thyroid function tests will be monitored as per the SOA. Abnormalities of thyroid function should be managed according to local guidance. If thyroid function cannot be adequately managed PegIFN treatment should be discontinued.
Hypoglycaemia/Hyperglycaemia/Diabetes Mellitus	Hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with PegIFN.	Participants with uncontrolled diabetes are excluded from this study. Blood glucose will be monitored throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Abnormalities of blood glucose should be managed according to local guidance. If blood glucose cannot be adequately managed PegIFN treatment should be discontinued.
Cardiovascular disorders: Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction	These have been associated with alfa interferon therapies, including PegIFN.	Patients with significant/unstable cardiac disease are excluded from the study. Participants will undergo an electrocardiogram (ECG) at screening and prior to PegIFN treatment. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued.
Retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision	These have been reported in rare instances with PegIFN.	All participants will have a baseline eye examination. Any participant complaining of a change in vision or a new visual disturbance will have an urgent eye examination and PegIFN should be discontinued.
Fever/Infections	Serious infections (bacterial, viral, fungal) and sepsis have been reported during treatment with alfa interferons including PegIFN.	Appropriate anti-infective therapy should be started immediately, and discontinuation of PegIFN should be considered
Pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis	These have been reported during therapy with PegIFN.	Participants with clinically significant pulmonary disease are excluded from the study. Any participant developing fever, cough, and dyspnoea or other respiratory symptoms must have a chest X ray taken. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.
Exacerbation or provocation of psoriasis.	Use of PegIFN has been associated with exacerbation or provocation of psoriasis.	In cases of onset or worsening of psoriatic lesions, discontinuation of therapy will be considered.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Development of autoantibodies and autoimmune disorders	These have been reported during treatment with alfa interferons.	Patients with signs or symptoms compatible with autoimmune disorders will be evaluated carefully, and the benefit-risk of continued interferon therapy should be re-assessed

1. The full benefit risk profile can be found in the Pegasys label

2.3.2. Benefit Assessment

Treatment of CHB with NAs 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 C HB 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.

Numerous studies have looked at predictors of response to PegIFN in CHB. Lower levels of baseline HBsAg consistently predict the highest response rates (RR) to PegIFN [Ren, 2019]. In study ISIS 505358-CS3 it was demonstrated that 4 weeks treatment with GSK3228836 weekly resulted in marked declines in serum HBsAg in the majority of participants, including four participants that achieved HBsAg seroclearance (<0.05 IU/mL), but subsequently relapsed. A GSK3228836 mediated reduction of serum HBsAg level prior to starting a short course of PegIFN therapy is expected to result in higher rates of HBsAg seroclearance and durability of response than if either agent was used alone and provide additional benefit over GSK3228836 treatment alone.

2.3.3. Overall Benefit: Risk Conclusion

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

3. OBJECTIVES AND ESTIMANDS

Objectives	Estimands and Endpoints
Primary	
Efficacy: To investigate the efficacy of two different durations of GSK3228836 followed by up to 24 weeks of PegIFN therapy in participants with CHB on stable NA therapy.	The main Estimand supporting the primary objective is defined as: • Population: Participants with CHB on stable NA therapy • Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy • Variable (Categorical): Participants achieving Sustained Virologic Response (SVR) (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment, without use of any rescue medication • Intercurrent Events: o Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN not related to any wide disruptive events (such as COVID-19 pandemic) will be ignored (treatment policy strategy). o Ineligibility to receive PegIFN will be ignored (treatment policy strategy) o Use of rescue medication (composite strategy). o Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled assuming they had not happened (hypothetical strategy). • Population Summary: The percentage of participants in each treatment group who achieve SVR, without use of any rescue medication The main primary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. Three supplementary Estimands are defined to support the primary objective: • The first supplementary Estimand is defined in the same way as the main Estimand, except the assessment time frame for patients achieving SVR will be 24 weeks after the actual end of treatment.

Objectives	Estimands and Endpoints
	Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. • The second supplementary Estimand is to understand the relationship between the PegIFN duration and achieving SVR for 24 weeks after the actual end of treatment, defined as: o Population: Participants with CHB on stable NA therapy o Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by 24 weeks of PegIFN therapy while on stable NA therapy o Variable: The relationship between SVR for 24 weeks after actual end of treatment and the duration of PegIFN received by participants o Intercurrent Events: ▪ Discontinuation and delayed start of, PegIFN, will be accounted to reflect the actual duration from the first to the last dose of PegIFN received (while-on-treatment strategy). ▪ Interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy) ▪ Discontinuation of, interruption in and non-adherence to GSK3228836 will be ignored (treatment policy strategy) ▪ Use of rescue medication (composite strategy). ▪ Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation and delayed start of, PegIFN will be handled with while-on-treatment strategy; wide disruptive events leading to interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy); wide disruptive events leading to discontinuation of, interruption in, and

Objectives	Estimands and Endpoints
	non-adherence to GSK3228836 will be ignored (treatment policy strategy). o Population Summary: The percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm • The second supplementary Estimand (supporting the primary objective in participants with CHB on stable NA therapy) is the percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm, taking into account discontinuation and delayed start of PegIFN, regardless of interruption in and other non-adherence to PegIFN, regardless of discontinuation of, interruption in and non-adherence to GSK3228836. • The third supplementary Estimand is defined in the same way as the main Estimand, except the strategy for intercurrent events of PegIFN ineligibility for more than 12 weeks and/or missing more than 12 doses of PegIFN will be principal stratum. This supplementary Estimand supporting the primary objective is the percentage of participants in each treatment arm that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in participants with CHB on stable NA therapy and receiving at least 12 doses of PegIFN, in the absence of rescue medication, regardless of discontinuation of, interruptions in or non-adherence to GSK3228836 had they not been affected by wide disruptive events.
Secondary	
Efficacy: To assess the efficacy of GSK3228836 and PegIFN sequential therapy on biomarkers and virus specific antibody responses	The Estimand supporting the objective is defined as: • Population: Participants with CHB on stable NA therapy; For the time to ALT normalisation variable, population will be aforementioned participants with baseline ALT >ULN. • Treatment: 300 mg GSK3228836 for 12, or 24 weeks followed by 24 weeks of PegIFN therapy while on stable NA therapy • Categorical Variables: o Achieving HBsAg <LLOQ and HBV DNA <LLOQ at two time points: (1) the planned end

	of treatment and (2) at the end of 24 weeks follow-up o Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL) at each scheduled visit or analysis window. o ALT normalisation (ALT ≤ULN) over time in absence of rescue medication in participants with baseline ALT >ULN Population summary is the percentage of participants in each category for each treatment group. o HBe antibody (anti-HBeAg) levels. • Continuous Variables: o Actual values and change from baseline over time for HBsAg, HBV DNA and HBeAg o Actual values and change from baseline over time for HBs antibody (anti-HBsAg) levels over time o Actual values and change from baseline over time for ALT Population summary is the mean values and the mean changes from baseline of each variable for participants in each treatment group. • Time to Event Variable: o Time to ALT normalisation in absence of rescue medication in participants with baseline ALT>ULN Population summary is the Turnbull's estimator for non-parametric estimation of Time to ALT normalisation in each treatment arm • Intercurrent Events: Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be ignored (treatment policy); PegIFN ineligibility will be ignored (treatment policy); Rescue medication will be ignored (treatment policy), except for ALT normalisation which can only be achieved in the absence of rescue medication; Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled with Treatment Policy Strategy. • The group of estimands supporting this objective is the population summary for each variable in each treatment arm in the population regardless of discontinuation of, interruption in or non-adherence to GSK3228836 and PegIFN, and regardless of rescue medication (except for ALT normalisation which can only be achieved in the absence of rescue medication) or PegIFN ineligibility.

Objectives	Estimands and Endpoints
Efficacy: To investigate the durability of virological response after sequential therapy with 12 weeks of GSK3228836 followed by 24 weeks of PegIFN in participants with CHB on stable NA therapy for up to 36 weeks off treatment.	The same definition as the above secondary estimand, focusing on the timepoints following the 24 weeks off-treatment period in the treatment arm of 300 mg GSK3228836 for 12 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
Efficacy: To compare efficacy between different treatment durations: 12 or 24 weeks of GSK3228836 followed by 24 weeks PegIFN	The same definition as the primary estimand except treatments and population summary are defined as: • Treatments: Arms 1 and 2. One treatment comparison between Arms 1 & 2 up to 24 weeks off-treatment • Population summary: difference in proportion of participants who achieve SVR between treatment arms The group of estimands supporting this objective in participants with CHB on stable NA therapy is the difference between treatment arms 1 and 2 in the proportion of participants that achieve SVR for 24 weeks after the planned end of sequential treatment, in the absence of rescue medication, regardless of ineligibility to receive PegIFN, regardless of discontinuation of, interruption in or non-adherence to GSK3228836 and PegIFN had they not been affected by wide disruptive events.
Exploratory	
Pharmacokinetics (PK) and PK-pharmacodynamic (PD) relationships of GSK3228836 and PegIFN: To evaluate PK, PK-efficacy relationship and PK-safety relationship	Efficacy assessments for PK/PD relationship include but not limited to • Categorical: virologic response, HBsAg level <LLOQ, HBV DNA level <LLOQ, and seroconversion (anti-HBsAg and anti-HBeAg); • Change from baseline: HBsAg, HBV DNA, anti-HBsAg and anti-HBeAg levels; • Time to event: virologic response (HBsAg and HBV DNA levels <LLOQ), nadir of HBsAg and HBV DNA, HBsAg level <LLOQ, HBV DNA level <LLOQ, seroconversion (anti-HBsAg and anti-HBeAg), and peak of ALT flares Safety assessments for PK/PD relationship include but not limited to vital signs, laboratory measurements and adverse events PK assessments include but not limited to $C\tau$ and terminal half-life ($t_{1/2}$).
Safety and Tolerability: To investigate the safety profile of sequential therapy with GSK3228836 (up to 24 weeks) followed by PegIFN (up to 24 weeks) in participants with CHB on stable NA therapy.	Clinical assessments including laboratory measurements and adverse events at timepoints specified in the SoA

Objectives	Estimands and Endpoints
CCI [redacted]	
Biomarkers: To assess the effect of GSK3228836 and PegIFN sequential therapy on immunological biomarkers. To describe the relationship(s) between virology biomarkers including HBsAg and immunological biomarkers.	Laboratory measurements of and correlation between the following: o Virological biomarkers, including specific viral parameters (HBsAg, HBeAg, HBV DNA, HBV RNA, HBcrAg) o Soluble biomarkers, including levels of circulating cytokines and chemokines o Markers of immune cell function, including relative frequencies of immune cell subsets among PBMCs, activation status as determined by phenotyping and gene expression patterns, and functional assays including HBV-specific cytokine and/or antibody production Timepoints are specified in the SoA

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIb, multi-centre, randomised, open-label study to assess the efficacy and safety of sequential treatment with GSK3228836 (300 mg/week for 12 or 24 weeks) followed by PegIFN (180 mcg/week for up to 24 weeks) in participants with CHB on stable NA therapy. During the GSK3228836 treatment period, a 300 mg loading dose will be administered on Day 4 and Day 11. Participants will continue their NA therapy for the duration of the study.

Participants will be randomised (1:1) into one of two parallel treatment arms.

1. 300 mg GSK3228836 once/week for 24 weeks (plus loading dose on Day 4 and 11) followed by PegIFN (180 mcg/week for up to 24 weeks). Participants will be followed up for an additional 24 weeks (off-treatment phase) once PegIFN treatment is complete.

2. 300 mg GSK3228836 once/week for 12 weeks (plus loading dose on Day 4 and 11) followed by PegIFN (180 mcg/week for up to 24 weeks). Participants will be followed up for an additional 36 weeks (off-treatment phase) once PegIFN treatment is complete.

The planned duration of GSK3228836 is 24 weeks and 12 weeks in Treatment Arm 1 and 2 respectively. If a participant prematurely discontinues GSK3228836 treatment the participant is encouraged to complete the SoA as per the planned GSK3228836 dosing period. At the end of the planned GSK3228836 dosing period, participants will be re-assessed for eligibility to start PegIFN treatment based on the label.

1. Participants immediately eligible for PegIFN will begin treatment

2. Participants who are not considered eligible will be re-assessed for eligibility and may delay start of PegIFN treatment for up to 12 weeks.

3. Participants who fail to meet PegIFN eligibility criteria by PegIFN Eligibility Week 13 (i.e. can no longer receive at least 12 weeks of PegIFN treatment) will not receive treatment with PegIFN.

Note: all participants are expected to end PegIFN treatment at the same time, regardless of when they start therapy (Treatment Group 1: all participants should complete treatment by Week 48; Treatment Group 2: Week 36).

As such, the planned treatment duration with PegIFN for participants on study 209348 may vary from a minimum of 12 weeks to a maximum of 24 weeks.

Participants will be randomised 1:1. Populations will be stratified based on HBsAg level (HBsAg ≤3 log IU/mL and >3 log IU/mL) and whether participants are HBeAg positive or negative. Lower HBsAg has been associated with increased likelihood of HBsAg loss in patients treated with PegIFN-containing regimens [Ren, 2019; Lee, 2018; Yeo, 2019]. With existing therapies different responses have also been observed in HBeAg positive and negative patient populations [Ren, 2019].

4.2. Scientific Rationale for Study Design

The rationale for the proposed study is to evaluate the potential of up to 48 weeks of sequential therapy with GSK3228836 and PegIFN to achieve sustained loss of HBsAg and HBV DNA in participants on stable NA therapy. Sustained virologic response is defined as undetectable levels of HBsAg and HBV DNA on treatment and maintaining this for a minimum of 24 weeks off-treatment (GSK3228836 and PegIFN).

This Phase IIb study has been designed to answer two questions which are considered critical to the overall development of GSK3228836 to achieve functional cure in patients with CHB:

1. Does sequential therapy with GSK3228836 (12 or 24 weeks) followed by up to 24 weeks of PegIFN result in improved rates of efficacy in NA-controlled CHB patients compared to GSK3228836 monotherapy?

2. Is the efficacy rate affected by the duration of treatment with GSK3228836 prior to starting PegIFN?

Addressing these questions is critical to our understanding of the potential for sequential therapy with immunomodulators to achieve functional cure in patients with CHB, and to optimise the duration of treatment with GSK3228836 prior to starting PegIFN (or other immunomodulators in future studies).

The proposed study will investigate efficacy of two different sequential treatment regimens with GSK3228836 and PegIFN (Pegasys; Hoffman La-Roche) in participants with CHB that are controlled with stable NA therapy.

Rationale for Patient Population

Participants will continue their NA therapy for the duration of the study. Liver flares (elevated ALT and related biomarkers) are common occurrences during treatment of CHB patients with interferon-containing therapies, and flares were also observed after 4 weeks of treatment with GSK3228836 in study ISIS 505358-CS3. Although we believe these flares to be therapeutic in nature and related to immune clearance of HBV from the liver, our intention is to manage the risk of possible exacerbations of hepatitis by first evaluating proof of concept (POC) in participants whose infection is already under control with stable NA therapy. Patients whose infection is controlled by NAs still have HBsAg detectable in serum due to the presence of HBV cccDNA and integrated DNA in infected hepatocytes. As such, this patient population has the best benefit:risk profile for early POC studies with experimental therapies.

Rationale for Selection of PegIFN

PegIFN is an immunomodulatory therapy approved for use in CHB patients. Rates of sustained loss of HBsAg following up to 48 weeks of treatment typically vary from 1- 9% at 24 weeks off-treatment follow-up when used in combination with NAs [Ren, 2019].

Rationale for Sequential Therapy (GSK3228836 followed by PegIFN)

Numerous studies have looked at predictors of response to PegIFN use in CHB. Lower levels of baseline HBsAg consistently predict the highest response rate to PegIFN in terms of HBsAg loss [Ren, 2019]. In study ISIS 505358-CS3, it was demonstrated that 4 weeks treatment with 150 mg or 300 mg GSK3228836 weekly (including loading doses) resulted in marked declines in serum HBsAg in the majority of participants, including 4 who experienced transient HBsAg seroclearance. The proposed design of study 209348 tests the hypothesis that using GSK3228836 to reduce serum HBsAg load prior to starting a

short course of PegIFN therapy will result in higher rates of sustained seroclearance than if either agent was used alone.

Rationale for Duration of GSK3228836 Treatment (12 or 24 weeks)

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 the majority of participants that responded to GSK3228836 in study ISIS 505358-CS3, serum HBsAg levels were still declining when treatment was stopped after 4 weeks. 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. In the proposed study, we will investigate 2 different durations of treatment with GSK3228836 (12 and 24 weeks at 300 mg/week) prior to starting PegIFN in order to optimise rates of sustained seroclearance.

Rationale for Duration of PegIFN (up to 24 weeks)

Current PegIFN treatment guidelines recommend 48 weeks treatment. In this study PegIFN will be administered for a maximum of 24 weeks duration. The rationale for administering a shorter duration of PegIFN is:

1. PegIFN administration is associated with numerous adverse effects and can be difficult to tolerate. This may in part explain the low use of PegIFN despite higher rates of HBeAg and HBsAg loss compared to nucleos(t)ide therapy.
2. Shorter duration of PegIFN may be more attractive to providers and patients. When GSK has sought advice from external experts on the role of PegIFN therapy in the context of our development program, the experts considered up to 24 weeks of PegIFN reasonable to keep the total duration of treatment i.e. approximately 1 year since both GSK3228836 and PegIFN are administered via subcutaneous injections.
3. Lower baseline levels of HBsAg prior to PegIFN therapy have been associated with better treatment outcomes. In this study, the preceding GSK3228836 treatment is anticipated to reduce HBsAg to lower or even undetectable levels prior to administration of PegIFN. In this context it is unclear whether longer duration of PegIFN would be beneficial.
4. A systematic review of treatment of CHB infection by PegIFN showed that PegIFN induced sustained biochemical and virological responses (ALT normalisation, HBeAg seroconversion, HBV DNA suppression) in about one-thirds of patients after 6 or 12 months of therapy. Importantly, the studies with longer duration of PegIFN treatment didn't show greater efficacy for the primary endpoints (virological responses), although the rate of HBsAg loss appeared slightly better with 12 months of treatment.

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

GSK3228836 Dose Levels, Frequency and Duration

GSK3228836 has been evaluated over a 4-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) on Day 4 and Day 11 was included in order to accelerate the achievement of steady state concentration in the liver to increase the likelihood of observing anti-HBV activity during such a short treatment duration. The loading schedule for GSK3228836 will be included in both treatment arms of study 209348.

To date, the highest dose of GSK3228836 evaluated was 2700 mg over 4 weeks (450 mg per injection including loading schedule; n=3) in healthy volunteers, and 1800 mg over 4 weeks (300 mg per injection including loading schedule; n=17) in participants with CHB. In 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 2 participants achieving HBsAg seroclearance by study Week 4. In both participants who achieved seroclearance by Week 4, 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. Taken together, the data suggest that a longer duration of GSK3228836 therapy may be required to both increase the rate of seroclearance and to achieve sustained seroclearance.

In study 209348, two different treatment durations with GSK3228836 (12 weeks and up to 24 weeks) will be studied prior to initiating treatment with PegIFN to assess differences in the efficacy endpoints (e.g., proportion of participants achieving seroclearance, durability of response):

1. 300 mg GSK3228836 for 24 weeks followed by up to 24 weeks of PegIFN;
2. 300 mg GSK3228836 for 12 weeks followed by up to 24 weeks of PegIFN;

PegIFN

PegIFN will be dosed according to the SoA (Section 1.3) for CHB patients for up to 24 weeks. Numerous clinical studies have evaluated the safety and tolerability of PegIFN when dosed with NAs (Ren, 2019). Except for telbivudine, which is contraindicated in the PegIFN label, no worsening of the safety and tolerability profile of PegIFN and/or commonly prescribed NAs has been reported when dosed concurrently in CHB patients.

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 NAs 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 NAs (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 NA-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 normalisation 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 NAs circulated in the blood stream with little binding to serum proteins [Bristol-Myers Squibb, 2018; Gilead 2018]. Tenofovir, entecavir, lamivudine, adefovir and telbivudine are predominantly renally eliminated from systemic circulation [Epivir, 2002; Kearney, 2004; Hepsera, 2012; Tyzeka, 2013; Entecavir, 2015; Bristol-Myers Squibb, 2018; Gilead, 2018]. These 5 drugs undergo a combination of glomerular filtration and tubular secretion, which have been reported to be mediated by one or more of the following transporters: the organic anion transporter (OAT) 1, OAT3, the organic cation transporter (OCT) 1, and OCT2 [Cihlar, 2001; Cihlar, 2004; Servais, 2006; Uwai, 2007; Minuesa, 2009; Yanxiao, 2011; Xu, 2013]. It has been shown that 2'-MOE ASO is neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2

[Yu, 2016; Shemesh, 2017]. Therefore, although GSK3228836 was shown to be extensively distributed into the kidney in non-clinical studies, it is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir, telbivudine, or other NAs.

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 NA-experienced, the majority of participants were on entecavir. Clinical data from this study suggest that co-administration of GSK3228836 is unlikely to impact efficacy and safety profiles. In Cohorts 1 to 3 in ISIS 505358-CS3 study, GSK3228836 was administered alone for 4 weeks, and then tenofovir dosing was started on Study Day 29 (7 days after the last dosing of GSK3228836). 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.

Clinical data suggest that co-administration of GSK3228836 is also unlikely to impact tenofovir PK. In Cohorts 1 to 3 (n=18) in the ISIS 505358-CS3 study, a daily dose of 300 mg tenofovir was initiated on Day 29 (7 days after the last dose of GSK3228836), and the tenofovir pre-dose plasma concentration was measured on Day 36, after tenofovir has been dosed for one week. Hepatic GSK3228836 concentration is at steady state after 4 weeks of dosing with the loading schedule, and there should be a substantial amount of GSK3228836 in the liver on Day 36 (2 weeks after the last dose of GSK3228836) due to the hepatic half-life of 3 weeks. Therefore, pre-dose tenofovir plasma concentration on Day 36 was deemed to be appropriate to provide preliminary evidence of impact of GSK3228836 on tenofovir PK. Pre-dose tenofovir plasma concentration on Day 36 was comparable to that in the public domain, suggesting that co-administration of GSK3228836 is unlikely to impact tenofovir PK.

Clinical data suggest that co-administration of GSK3228836 is unlikely to impact entecavir PK. In Cohort 4 in ISIS 505358-CS3 study, entecavir was co-administered with GSK3228836 throughout the treatment period in 4 participants and administered alone in 2 participants (participants on placebo). Entecavir concentration was comparable in participants with GSK3228836 (n=4) and without GSK3228836 (n=2), and comparable to that in public domain, suggesting that co-administration of GSK3228836 is unlikely to impact entecavir PK

4.4. End of Study Definition

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

A participant is considered to have completed the study if they completed all phases of the study for which they were eligible, including the last visit.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Participants are eligible to be included in the study only if all of the following criteria apply:

5.1. Inclusion Criteria

AGE
1. At least 18 to 75 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 are eligible to be treated with PegIFN (Table 8) 3. Documented chronic HBV infection ≥6 months prior to screening AND currently receiving stable NA therapy except telbivudine, defined as no changes to their NA regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study 4. Plasma or serum HBsAg concentration >100 IU/mL 5. Plasma or serum HBV DNA <90 IU/mL 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) as defined in Section 10.4 Contraception and Barrier Guidance

2. 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

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention, see Section 10.2.
    - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Additional requirements for pregnancy testing during and after study intervention are located in Section 10.2.

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

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

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

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, autoimmune disease, or coagulopathy) or physical examination
2. Co-infection with:
    a. Current or past history of Hepatitis C virus (HCV)
    b. Human immunodeficiency virus (HIV)
    c. Hepatitis D virus (HDV)
3. History of or suspected liver cirrhosis and/or evidence of cirrhosis as determined by
    a. Both Aspartate aminotransferase (AST)-Platelet Index (APRI) >2 and FibroSure/FibroTest result >0.7
        i. If only one parameter (APRI or FibroSure/FibroTest) result is positive, a discussion with the Medical Monitor is required before inclusion in study is permitted
    b. Regardless of APRI or Fibrosure/FibroTest score, if the participant meets one of the following historical criteria, they will be excluded from the study
        i. Liver biopsy (i.e., Metavir Score F4)
        ii. Liver stiffness >12 kPa
4. Diagnosed or suspected hepatocellular carcinoma as evidenced by the following
    a. Alpha-fetoprotein concentration ≥200 ng/mL
    b. If the screening alpha fetoprotein concentration is ≥50 ng/mL and <200 ng/mL, the absence of liver mass must be documented by imaging within 6 months before randomisation
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. Poorly controlled thyroid dysfunction or abnormal thyroid stimulating hormone (TSH) levels
9. Positive (or borderline positive) Anti-neutrophil cytoplasmic antibody (ANCA) at screening:

a. Participants that meet these criteria may be considered for inclusion in the study following:
    i. Analysis of MPO-ANCA [perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)] and PR3-ANCA [classical anti-neutrophil cytoplasmic antibodies (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

10. Low C3 at screening AND evidence of past history or current manifestations of vasculitic/inflammatory/auto-immune conditions

    a. All participants with low C3 at screening should have their medical history discussed with the Medical Monitor prior to enrolment

11. History of alcohol or drug abuse/dependence
    a. Current alcohol use as judged by investigator to potentially interfere with participant compliance
    b. History of or current drug abuse/dependence as judged by the investigator to potentially interfere with participant compliance
        i. Refers to illicit drugs and substances with abuse potential. Medications that are used by the participant as directed, whether over-the-counter or through prescription, are acceptable and would not meet the exclusion criteria
12. Pre-existing severe psychiatric condition or a history of severe psychiatric disorders, including severe depression, suicidal ideation and attempted suicide.

PRIOR/CONCOMITANT THERAPY

13. 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.
14. Participants for whom immunosuppressive treatment is not advised, including therapeutic doses of steroids.
15. Patients with prior treatment with Pegylated interferon or interferon are excluded.
16. Participants requiring anti-coagulation therapies (for example warfarin, Factor Xa inhibitors or anti-platelet agents like clopidogrel)
17. Participants currently taking, or took within 6 months of screening, telbivudine

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

18. 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).

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

DIAGNOSTIC ASSESSMENTS
20. Fridericia's QT correction formula (QTcF) ≥450 msec (if single ECG at screening shows QTcF ≥450 msec, a mean of triplicate measurements should be used to confirm that participant meets exclusion criterion). 21. Laboratory results as follows a. Serum albumin <3.5 g/dL b. Glomerular filtration rate (GFR) <60 mL/min /1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiologic Collaboration formula (for Japan, Japanese Society of Nephrology - Chronic Kidney Disease Initiative equation). c. International normalised ratio (INR) >1.25 d. Platelet count <140 X 10^9/L e. Absolute neutrophil count (ANC) <1.5 x 109 cells/L f. Baseline haemoglobin <10 g/dL g. Total bilirubin >1.25 x ULN. 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 h. 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. 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 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
22. History of/sensitivity to GSK3228836 or interferon-containing therapies, 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. Inclusion and Exclusion Criteria for PegIFN

Participants who permanently discontinue GSK3228836 due to a liver stopping event (Section 7.1.1) are not eligible for treatment with PegIFN.

Participants who had GSK3228836 dosing held or whose dose was reduced due to Protocol defined liver monitoring criteria (Section 7.1.1) are eligible for PegIFN treatment only if:

a. ALT is <5xULN and bilirubin/INR are ≤baseline or ULN (whichever is higher) at PegIFN eligibility assessment
AND
b. Additional lab assessments performed do not suggest drug-induced liver injury (DILI) or other condition contraindicated for treatment in the PegIFN label.

For participants who do not meet both of these criteria, eligibility for PegIFN should be determined by the investigator based upon a risk/benefit assessment and the following PegIFN eligibility criteria (Table 8).

Note: If local prescribing PegIFN guidelines are more stringent than the criteria below, follow the most stringent criteria.

- ALT <5 x ULN
- Platelets >90 x 10^9/L
- Absolute Neutrophil Count (ANC) >1.5 x 10^9/L
- Haemoglobin ≥10 g/dL

In addition:

- TSH + T4 should be confirmed to be normal and/or adequately controlled
- The absence of severe psychiatric condition
- An ophthalmologic examination should have been conducted at screening (or results from a prior ophthalmological examination within 3 months of screening should have been available).

Table 8 Eligibility Criteria to start PegIFN

Baseline Laboratory Assessment	Inclusion Criteria
i) Platelets	>90 x 10^9 cells/L
ii) ANC	>1.5 x 10^9 cells/L
iii) Haemoglobin	>10 g/dL
iv) ALT	<5 x ULN
v) TSH/T4	Within normal range or adequately controlled
vi) Neuropsychiatric Assessment	No severe psychiatric condition
vii) Ocular Exam	No condition contraindicated for PegIFN, however periodic examinations maybe required based upon screening assessment (refer to Section 8.2.2)

5.4. Lifestyle Considerations

5.4.1. 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 vaporisers) will not be permitted while they are in the clinical unit.

5.4.2. 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.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. 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 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.

5.6. Criteria for Temporarily Delaying Administration of Study Intervention

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

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

Study Treatment

Study Treatment		
Product Name:	GSK3228836	PegIFN
Formulation Description:	Clear colourless to slightly yellow solution	Injection for subcutaneous use. The commercial product is used unmodified, except a label is applied to indicate clinical investigational use.
Dosage Form:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	150 mg/mL; 1.0 mL nominal volume per vial (minimal overfill per vial)	180 mcg/0.5 mL; pre-filled syringe
Route/Administration/Duration:	SC, multiple (once weekly up to 24 weeks, plus loading doses)	180 mcg/week, SC, up to 24 weeks
Dosing Instructions:	Administer two SC injections for 300 mg dose.	Administer SC injection; refer to label
Manufacturer/Source of Procurement:	GSK GlaxoSmithKline Manufacturing SpA, Parma (Italy)	F Hoffmann-La Roche AG, Wurmisweg, 4303 Kaiseraugst, Switzerland.
Method for Individualising Dosage	Dispensing into syringes	Pre-filled syringe that contains graduation marks corresponding to 180 micrograms (mcg), 135 mcg and 90 mcg

SC=subcutaneous;

GSK3228836 injection instructions

The site of GSK3228836 injection will be recorded for each participant and dose(s). Sites of GSK3228836 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

GSK3228836 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.

PegIFN injection instructions

PegIFN is administered by subcutaneous injection in the abdomen or thigh. PegIFN should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discoloured.

A participant may self-inject PegIFN only if the physician determines that it is appropriate, and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique.

Discard the unused portion in excess of the labelled volume. Use only one vial or prefilled syringe or disposable auto-injector per dose.

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 authorised 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 authorised 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 (SRM).

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 Minimise Bias: Randomisation and Blinding

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

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

Participants will be randomised in a 1:1 ratio to receive study intervention. Investigators and the participants will be unblinded to study intervention throughout the course of the study. Allocation will be concealed by central blocking to protect against foreknowledge of allocation pre-randomisation.

GSK is unblinded however the risk of potential bias will be mitigated by the following steps:

- Dummy randomisation schedule will be used by Biostatistics during preparatory programming activities, although this will not completely mask treatment assignment due to the different visit/regimen schedules for each arm.
- Where feasible, limit the central teams exposure to virological biomarkers including HbsAg, HbsAb and HBV DNA.

- Details will be included in separate blinding plans.

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

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

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Participants may self-inject PegIFN during specified visits in the PegIFN treatment phase (see Table 4) as allowed per country requirements. Site staff will telephone to confirm the dose as described above.

6.5. Dose Modification

Dose modifications of GSK3228836 are not planned for this study. Dose modifications of PegIFN are allowed per Section 7.2.

6.6. 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:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3228836 can no longer be detected systemically (at least 105 days).
- 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).

- Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (CRF).

Decisions regarding dose interruptions or dose modifications of PegIFN 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 NA therapy, 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 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 for GSK3228836 are not permitted during the study:

- 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
- Creatine-containing gym supplements
- Anticoagulation therapy
- Anti-platelet therapy

Refer to the local label for prohibited concomitant medications for PegIFN [Pegasys, 2017]. Telbivudine is contraindicated in the PegIFN label; the combination of telbivudine with interferon products (such as peginterferon) to treat hepatitis may increase the risk of peripheral neuropathy [Tyzeka, 2013].

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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. 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- Section 7.2), participants should be monitored until laboratory abnormalities resolve, stabilise, or return to within baseline values 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. GSK3228836 Dose Modification and Stopping Criteria

7.1.1. GSK3228836 Liver Chemistry 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. Restart/re-challenge guidelines are presented in Section 10.6 (Appendix 6).

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

- a participant meets one of the conditions outlined in Table 9.
- 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 9 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, stabilise, 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, stabilise, 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 9 GSK3228836 Liver Chemistry Monitoring and Stopping Criteria

ALT Level	Monitoring Plan	Discontinuation
10 x ULN ≤ALT <12 x ULN **and** Bilirubin ≤1.5 x ULN **and** INR ≤1.5 (if available)	Monitor twice weekly Additional lab assessments	Permanently discontinue IMP if ALT >10 x ULN >4 weeks
ALT ≥12 x ULN **and** Bilirubin ≤1.5 x ULN **and** INR ≤1.5 (if available)	Hold dose Monitor twice weekly Additional lab assessments if not already done Take off hold: GSK3228836 150 mg SC weekly when ALT <10 x ULN; increasing dose to 300 mg (if applicable) should be agreed with Medical Monitor	Permanently discontinue IMP if any of the following apply: • ALT ≥10 x ULN >4 weeks • ALT ≥12 x ULN recurs after IMP taken off hold
ALT ≥3 x ULN **and** 1.5 x ULN <bilirubin ≤2 x ULN (>35% direct) **and** INR ≤1.5 (if available)	Hold dose Monitor twice weekly Additional lab assessments if not already done Take off hold: GSK3228836 150 mg SC weekly when bilirubin returns to <1.5 x 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: 1.5 x ULN <bilirubin ≤2 x ULN (>35% direct) **And** INR ≤1.5 (if available)
ALT ≥3 x ULN **and** any of the following apply: • bilirubin >2 x 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.
- Deterioration considered clinically significant from the baseline in the liver parameters must be confirmed by retesting ALT, total bilirubin, direct bilirubin and INR (if available).
- If one criterion in the list above is met and confirmed by retesting, further treatment may be discontinued for this participant after discussion with the Medical Monitor. Results of retesting must be evaluated before the next dose is administered.
- Monitor participant until liver chemistry abnormalities resolve, stabilise, or return to within baseline values.
- Cases such as Gilbert syndrome, where baseline bilirubin values are high, should be discussed with the Medical Monitor, to assess if it is a case of DILI or the participant may continue with dosing.

The procedures listed below are to be followed if a participant meets any of the liver chemistry stopping criteria defined in Table 9:

Notify the Medical Monitor within 24 hours of learning of the abnormality to confirm the participant's study treatment cessation and follow-up.

Complete the Liver Event CRF.

Complete the "Safety Follow-up Procedures" listed below.

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

Viral hepatitis serology including:

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

- Obtain a blood sample for pharmacokinetic (PK) analysis as soon as possible following the occurrence of an event. Record the date/time of the PK blood sample collection and the date/time of the last dose of study treatment prior to blood sample collection on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. Instructions for sample handling and shipping are included in the 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]), if available.
- Liver imaging (ultrasound, magnetic resonance, or computerised 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. GSK3228836 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 the lower limit of normal (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 participants 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, stabilise, or return to within baseline values.

Table 10 GSK3228836 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 ≤ Platelets <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/non-steroidal anti-inflammatory drugs/anticoagulants

7.1.3. GSK3228836 Drug Induced Kidney Injury (Renal) Stopping Criteria

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

- Persistent ACR ≥0.03 mg/mg (≥30 mg/g)
- Blood in urinalysis ≥5 red blood cells (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, antinuclear antibody [ANA], double stranded deoxyribonucleic acid [dsDNA], cryoglobulins), serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP), and complement panel (C3, C4, C5a, and Bb). Further evaluation and actions should be determined by the investigator in consultation with the Medical Monitor.

Treatment Hold/Treatment Discontinuation

- Hold study treatment in participants who develop ACR ≥0.5 mg/mg (500 mg/g), or eGFR >25% reduction from pre-dose range, pending consultation with the Medical Monitor and further evaluation of the cause.
    - If a dose is held, once eGFR increases to within baseline, ACR decreases to <0.5 mg/mg (500 mg/g), or the underlying cause of the decline in renal

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

7.1.4. GSK3228836-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.

- **Persisting & deteriorating longitudinal trends in change from baseline for C3 and/or C4 defined as:**
    - If participant's baseline C3 and/or C4 is ***within*** the lab's normal range at baseline: there is a sequential decline in C3 and/or C4 once levels have fallen below LLN for ≥4 weeks OR
    - 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
    - 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
    - There is an associated ≥***3-fold increase*** in Bb and/or C5a from participant's baseline OR
    - 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

  - There are associated clinical sequelae, for example, ≥2 + haematuria; increasing urine ACR; vasculitic or purpuric rash; peripheral neuropathy; jaundice OR
  - There is new cANCA or pANCA positivity

- **Persisting & deteriorating longitudinal trends in change from baseline for Bb and/or C5a where**
  - There is a ≥3-fold increase in Bb and/or C5a over baseline AND
  - This is persisting or increasing week on week in sequential data plots OR
  - 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
  - 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
  - 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, DIVI, vasculitis or autoimmunity regardless of biomarkers changes or persistence.

7.2. PegIFN Dose Modification and Stopping Criteria

Discontinuation of treatment with PegIFN should be considered in any participant with an adverse event where the risk of continued treatment outweighs the potential benefit (see Section 2.3.1).

When dose modification is required for moderate to severe adverse reactions, both clinical and laboratory, initial dose reduction to 135 mcg is generally adequate (Pegasys PI, 2017). However, in some cases a reduction to 90 mcg is necessary. Dose increase to, or towards the original dose may be considered if the adverse reaction abates.

7.2.1. PegIFN Haematological Dose Modification and Discontinuation Guidelines

Table 11 PegIFN Haematological Dose Modification Guidelines[1]

Laboratory Values	Reduce PegIFN dose if:	Discontinue PegIFN if:
Absolute Neutrophil Count (ANC)	<750 cells/mm^3 reduce to 135 mcg (in some cases reduction to 90 mcg may be necessary)	<500 cells/mm^3 treatment should be suspended until ANC values return to more than 1000 cell/mm^3 Initially reinstitute at 90 mcg and monitor ANC
Platelet Count	<50 x 10^9 cells/L reduce to 90 mcg	<25 X 10^9 cells/L
Haemoglobin		Hb <8.5 g/dL

1. Not applicable to sites in Japan

After dose reduction or discontinuation, the patient should be monitored weekly until lab values return to within baseline values.

7.2.2. PegIFN ALT Elevation Dose Modification and Discontinuation Guidelines

In participants with elevations in ALT (greater than 5 x ULN), more frequent monitoring of liver function should be performed and consideration should be given to either reducing the dose to 135 mcg or temporarily discontinuing treatment. After reduction or withholding, therapy can be resumed after ALT flares subside.

In participants with persistent, severe hepatitis B flares (ALT greater than 10 X ULN), consideration should be given to discontinuation of treatment. If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued. When practicable, abnormal laboratory results should be confirmed as soon as possible following notification of the investigator.

7.2.3. Psychiatric Disorder Dose Modification and Discontinuation Guidelines

Participants will be monitored for evidence of depression and other psychiatric symptoms by the Columbia Suicide-Severity Rating Scale (C-SSRS) and Beck Depression Inventory-II (BDI-II). Participants displaying new or worsening symptoms of depression will be managed as per Table 12.

If new or worsening psychiatric symptoms (other than depression) are identified or if suicidal ideation is identified, PegIFN should be discontinued and the participant followed up with psychiatric intervention as appropriate.

Table 12 PegIFN Dose Modification and Stopping Criteria for Depression

Depression Severity	Initial Management (4-8 weeks)		Depression Status		
	Dose Modification	Visit Schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	(See moderate or severe depression)
Moderate	Decrease PegIFN dose to 135 mcg (in some cases reduction to 90 mcg may be needed)	Evaluate once weekly (office visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	(See severe depression)
Severe	Discontinue PegIFN permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

7.3. Study Intervention Restart or Rechallenge after stopping criteria met

GSK3228836 rechallenge after stopping criteria are met (i.e., study treatment discontinued) by any participant in this study is not allowed.

GSK3228836 restart may be considered only for liver events as follows:

Restart Following Transient Resolving Liver Stopping Events Not Related to GSK3228836

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 <3 x ULN).
    - 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, if required, of study intervention restart has been obtained.

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

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

For treatment that has been placed on hold, please follow the guidelines above (Section 7.1.1 to Section 7.2.3).

7.4. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- The investigator may ask participants to withdraw from study treatment, but continue with post-treatment follow up visits instead of withdrawing completely from the study.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.5. Lost to Follow Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised 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 utilised 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 GSK3228836 treatment followed by PegIFN on serum HBsAg levels in participants with CHB. The primary efficacy endpoint is achieving serum HBsAg level <LLOQ.

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. 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 exam will be conducted at all other time points.

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

8.2.2. Ophthalmologic Examination for PegIFN

- All patients should receive an eye examination prior to initiation of PegIFN (SoA, Table 1). Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during PegIFN therapy. Any patient who develops ocular symptoms must have a prompt and complete eye examination.

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

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 Section 10.2 (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 Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.6. Injection Site Reactions

Injection Site Reactions (ISRs) are any experiences which occur at the site of injection of the study treatment. Participants will be monitored closely for ISRs and ISRs should be recorded as AEs. Injection site reactions will be graded according to the criteria provided in the Division of AIDS (DAIDS) grading table (see Section 10.3 (Appendix 3)).

8.2.7. Suicidal Ideation and Behaviour Risk Monitoring

PegIFN is related to products with an increased risk of suicidal ideation or behaviour.

Participants being treated with PegIFN should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Participants who experience signs of suicidal ideation or behaviour, should undergo a risk assessment. All factors contributing to Suicidal Ideation and Behaviour should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with PegIFN should be alerted about the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behaviour will be monitored during this study using the C-SSRS and BDI-II.

8.2.7.1. Columbia Suicide-Severity Rating Scale (C-SSRS)

Assessment of treatment-emergent suicidality will be monitored during this study using the C-SSRS. The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences, and all subsequent questioning in relation to the last assessment. The C-SSRS is to be administered as a patient completed questionnaire specified in the SoA (Section 1.3).

8.2.7.2. Beck Depression Inventory-II (BDI-II)

The BDI-II is a 21-item questionnaire used to assess the intensity of depression in clinical and normal patients. The questionnaire will be administered by appropriate site personnel as specified in the SoA (Section 1.3).

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

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

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

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

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

All AEs and SAEs will be collected from the signing of the informed consent 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 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 Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.5 Lost to Follow Up). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female 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 Section 10.4 (Appendix 4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

8.3.6. Cardiovascular and Death Events

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

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

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

8.3.7. GSK3228836-Related Adverse Events of Special Interest

8.3.7.1. ALT Increases

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

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

A monitoring strategy of ALT is presented in Section 7.1.1

8.3.7.2. Vascular Inflammation and Complement Activation

Inflammatory and immune changes are recognised 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 7.1.4

8.3.7.3. Thrombocytopenia

Thrombocytopenia, decreased platelets, is a well-recognised 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 7.1.2

8.3.7.4. Renal Injury

Glomerulonephritis, including rapidly progressing glomerulonephritis, has been reported with ASOs and is thought to be a result of the proinflammatory effect of ASOs. Accumulation of antisense oligonucleotides in proximal tubule cells of the kidney, is

thought to sometimes lead to increased tubular proteinuria (as described in preclinical studies). Increases in urine protein have been described in the clinic.

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

8.3.7.5. Injection Site Reactions

Injection site reactions were the most commonly reported treatment-related adverse event in previous studies with GSK3228836. Injection site reactions included, but were not limited to, pain, erythema and pruritus. Injection site reactions will be assessed at all dosing visits and, if present, should be reported as AEs.

8.4. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

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

8.5. Pharmacokinetics

Blood samples will be collected pre-dose for measurement of GSK3228836 and PegIFN trough plasma concentrations and plasma concentrations during the terminal elimination phase as specified in the SoA (see Section 1.3). PK samples collected during the off treatment period at visits specified in the SoA can be collected at any time.

- 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 PegIFN, and to 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.

8.6. Biomarkers

Collection of blood samples for exploratory biomarker research is also part of this study. These exploratory biomarker samples will be collected to evaluate the pathobiology of CHB, the participants' response to GSK3228836, or the participants' response to the virus following treatment. In addition, continuing research may identify other proteins,

transcripts or biomarkers related to GSK3228836 treatment, the response to GSK3228836 or the pathogenesis of CHB, which will be evaluated in these samples.

- Blood samples, including serum, plasma, PBMCs and PAXgene tubes will be collected to evaluate virologic and immune biomarkers related to the pathogenesis of CHB and the participants' response to GSK3228836, PegIFN or both. Samples will be collected according to the schedule described in the SoA and as detailed in the study reference manual provided separately to sites.
- GSK may store samples for up to 15 years after the end of the study to achieve study objectives and for follow-up exploration of the laboratory findings and/or AEs (e.g., measurement of cytokine or chemokine levels, measurement of antibodies, etc.). The archive samples may also be used for studying biomarkers that may be affected by treatment, such as HBcrAg, indoleamine 2, 3 dioxygenase (IDO), or other immune-related responses. Additionally, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of chronic hepatitis B or other diseases, the development of related or new treatments or research methods.

For China, see Appendix 7: Country-specific requirements on biomarkers.

8.7. 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).

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

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

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

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

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.

8.8. Independent Data Monitoring Committee

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

8.9. Internal Safety Review Team (SRT)

A separate internal safety review team will meet to review all participants safety data on a regular basis to ensure any new or emerging safety issues are identified and managed in a timely manner.

8.10. Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation 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 investigate the effectiveness of GSK3228836 and PegIFN sequential therapy in CHB patients on stable NA therapy. The primary endpoint is achieving a sustained virologic response (SVR, HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 and PegIFN sequential treatment in the absence of rescue medication. Rescue medication is defined as any medication initiated for the purpose of antiviral suppression other than the background stable NA therapy. A secondary objective is to compare the efficacy between 24 and 12 weeks of GSK3228836 treatment followed by PegIFN for up to 24 weeks, measured by the proportion of participants that achieve virologic response at the planned end of sequential treatment and sustained for six months or more post-treatment. The aim of the study is to provide evidence for efficacy of GSK3228836 and PegIFN sequential therapy in reaching sustained virologic response, and to inform selection of treatment regimen for Phase III trials based on the comparison between the two arms.

The primary aim for the study is descriptive, hence no formal hypothesis testing is planned. A probability inference approach will be used for decision-making. The primary assessment of interest is the SVR rate of each treatment group. The point estimates for SVR and 95% credible intervals will be calculated using a Bayesian probability approach; in addition, posterior probabilities that the true SVR in each treatment arm is greater than a range of clinically meaningful response rates will be provided.

Comparisons between treatment arms as defined in the key secondary objectives will be assessed using probability inference approaches.

9.2. Sample Size Determination

For the entire study, approximately 100 participants will be enrolled and randomised to achieve approximately 50 participants in each treatment group:

- 24 weeks treatment of GSK3228836 followed by up to 24 weeks treatment of PegIFN
- 12 weeks treatment of GSK3228836 followed by up to 24 weeks treatment of PegIFN

It is assumed that the number of responders follows a Binomial distribution, with a weakly informative prior (Beta (0.5, 0.5)) for the true RR. The precision for a range of RRs with 95% credible intervals are shown in Table 13.

Table 13 95% Credible Interval of Response Rate

Number of Responders	Response Rate	95% Credible Interval*
9	18%	9% - 30%
10	20%	11% - 33%
11	22%	12% - 35%
12	24%	14% - 37%
13	26%	15% - 39%
14	28%	17% - 41%
15	30%	19% - 44%
16	32%	20% - 46%
17	34%	22%-48%
18	36%	24% - 50%
19	38%	26% - 52%
20	40%	27% - 54%

*95% equal-tailed interval

The historical RR of a combination therapy of NA and PegIFN was 10% [Ren, 2019; Lee, 2018]. The lower bounds of 95% credible intervals will exclude the RR of 10% if observed RR is greater than or equal to 20% (10 responders out of 50 participants) in an arm.

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

The operating characteristics based on at least 65% posterior confidence that the true rate exceeds a threshold of interest, are shown in Table 14, for various sample sizes, and true cure rates. The operating characteristics shown are based on a Bayesian inference without consideration of baseline stratification factors.

Table 14 End of Study Operating Characteristics by Sample Size

Criterion	Sample size per arm	Minimum number (%) of responders required to meet Criterion	Probability of meeting criterion under various assumptions			
			True SVR rate = 20%	True SVR rate = 30%	True SVR rate = 35%	True SVR rate = 40%
Probability (true response rate > 20%) > 65%	30	7 (23%)	39%	84%	94%	98%
	40	9 (23%)	41%	89%	97%	99%
	50	12 (24%)	29%	86%	97%	99%
	60	14 (23%)	31%	90%	98%	100%
Probability (true response rate > 30%) > 65%	30	10 (33%)	6%	41%	64%	82%
	40	14 (35%)	2%	30%	56%	79%
	50	17 (34%)	1%	32%	61%	84%
	60	20 (33%)	1%	33%	65%	88%
Probability (true response rate > 40%) > 65%	30	14 (47%)	0%	4%	13%	29%
	40	18 (45%)	0%	3%	12%	31%
	50	22 (44%)	0%	3%	12%	33%
	60	26 (43%)	0%	2%	11%	34%

Based on these operating characteristics, for a true RR of 30%, the proposed sample size of n=50 for each arm has ~86% probability of confirming a true response of at least 20%, and if the true rate is 40%, there is an 84% chance of confirming a true response of at least 30%. There are no plans for sample size re-estimation.

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility
Enrolled	○ All participants who passed screening and entered the study ○ Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study
Intent-to-treat (ITT)	• All randomised participants. • This population will be based on the treatment the participant was randomised to • Any participant who receives a treatment randomisation number will be considered to have been randomised
Safety	• All participants who were randomised and received at least one dose of study treatment • This population will be based on the treatment the participant received.
Pharmacokinetics (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
Pharmacodynamics (PD)	All participants in the Safety population for whom a Pharmacodynamic sample was obtained and analysed.

9.4. Statistical Analyses

The statistical analysis plan critical component will be finalised prior to the first patient first visit. The full statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. No adjustments will be made for multiplicity.

9.4.1. General Considerations

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

The primary analysis for the primary objective will be conducted once the last participant has completed the Week 72 visit and database lock has achieved.

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

HBsAg and HBV DNA from the week of end-of-treatment to Off-Treatment Week 24 will be used to assess the primary endpoint for each arm.

9.4.2.1. Main Estimands

Main Estimands supporting the primary objective are defined as:

- Population: Participants with CHB on stable NA therapy
- Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy
- Variable (Categorical): Participants achieving Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment, without use of any rescue medication
- Intercurrent Events:
    - Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN not related to any wide disruptive events (such as COVID-19 pandemic) will be ignored (treatment policy strategy).
    - Ineligibility to receive PegIFN will be ignored (treatment policy strategy)
    - Use of rescue medication (composite strategy).
    - Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled assuming they had not happened (hypothetical strategy).
- Population-level Summary: The percentage of participants in each treatment group who achieve Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment, without use of any rescue medication

9.4.2.2. Supplementary Estimands

Three supplementary Estimands are defined to support the primary objective.

The first supplementary Estimand is defined in the same way as the main Estimand, except the assessment time frame for patients achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in or non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events.

The second supplementary Estimand is to understand the relationship between the PegIFN duration and achieving SVR for 24 weeks after the actual end of treatment, defined as:

- Population: Participants with CHB on stable NA therapy
- Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy
- Variable: The relationship between SVR for 24 weeks after actual end of treatment and of PegIFN received by participants before completion or discontinuation of each treatment
- Intercurrent Events:
    - Discontinuation and delayed start of PegIFN will be accounted to reflect the actual duration from the first to the last dose of PegIFN received (while-on-treatment strategy).
    - Interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy).
    - Discontinuation of, interruption in and non-adherence to GSK3228836 will be ignored (treatment policy strategy).
    - Use of rescue medication (composite strategy).
    - Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation and delayed start of PegIFN will be handled with while-on-treatment strategy; wide disruptive events leading to interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy); wide disruptive events leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be ignored (treatment policy strategy).
- Population Summary: The percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping (groupings to be defined in the RAP) in each treatment arm.

The second supplementary Estimand (supporting the primary objective in participants with CHB on stable NA therapy) is percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm, taking into account discontinuation and delayed start of PegIFN, regardless of interruption in and other non-adherence to PegIFN, regardless of discontinuation of, interruption in and non-adherence to GSK3228836. The PegIFN treatment duration will support interpretation of the percentage of participants achieving SVR for 24 weeks after the actual end of treatment, especially if participants discontinue from PegIFN early or delay start of PegIFN due to ineligibility.

The third supplementary Estimand is defined in the same way as the main Estimand, except the strategy for intercurrent events of PegIFN ineligibility for more than 12 weeks (i.e. can no longer receive at least 12 weeks of PegIFN treatment) and/or missing at least 12 doses

of PegIFN will be principal stratum. This supplementary Estimand supporting the primary objective is the percentage of participants in each treatment arm that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in participants with CHB on stable NA therapy and receiving at least 12 doses of PegIFN, in the absence of rescue medication, regardless of discontinuation of, interruptions in or non-adherence to GSK3228836 had they not been affected by wide disruptive events.

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

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

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

2) For the main estimand supporting the primary objective, a sensitivity analysis will be performed using the Bayesian model described in Section 9.4.2.4 assuming missing at random whereby a participant's response will be imputed using all available data (on and off treatment values) for participants who completed the study.

9.4.2.4. Primary Analyses

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

A Bayesian hierarchical model will be used to estimate the posterior probability of sustained virologic RR incorporating the baseline stratification factors [Jones, 2011]. Main effects for each of the 2 strata will be included as independent parameters in the model denoted γ_k (k = 1, 2); Interactions between the 2 levels of stratification factors are anticipated to be small, and so will be modelled as exchangeable random effects (ψ_g) centred on zero to enable borrowing of information about the RR across strata.

$$\theta_g = \tau + \gamma_1 I_{\{B1+\}} + \gamma_2 I_{\{B2+\}} + \psi_g$$

$$\tau \sim Normal\ (0, 10^6)$$

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

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

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

Where θ_g is defined as the log odds of treatment response, index g =1, 2, 3, and 4 on the random effect ψ refers to each of the 4 possible combinations of strata levels. The parameter $\tau + \psi_1$ represents the treatment effect in reference stratum (HBsAg ≤3 log IU/mL and Negative HBeAg), while g denotes a random stratum effect in group g.

The four stratum and representation of the two baseline stratification factors B_1 and B_2 in the model are shown in Table 15.

Table 15 Baseline Stratification Factors for Four Stratum

Stratum	B_1: HBsAg	B_2: HBeAg
1: HBsAg <3 log IU/mL and Negative HBeAg	B_{1-} (≤3 log IU/mL)	B_{2-} (Negative)
2: HBsAg ≥3 log IU/mL and Negative HBeAg	B_{1+} (>3 log IU/mL)	B_{2-} (Negative)
3: HBsAg <3 log IU/mL and Positive HBeAg	B_{1-} (≤3 log IU/mL)	B_{2+} (Positive)
4: HBsAg ≥3 log IU/mL and Positive HBeAg	B_{1+} (>3 log IU/mL)	B_{2+} (Positive)

The point estimates of sustained virologic RR in each treatment arms with 95% credible intervals will be calculated. Handling of withdrawal from study and missing HBsAg and HBV DNA data is described in Section 9.4.2.3.

Posterior probability of sustained virologic RR exceeding a range of clinically meaningful RRs will be generated using the model specified.

9.4.3. Secondary Endpoints

9.4.3.1. Secondary Estimands

Three groups of estimands are defined for the secondary efficacy objectives. Categorical definitions for secondary analyses will be provided in the RAP.

1. Estimands supporting secondary objective of assessing the efficacy of GSK3228836 and PegIFN sequential therapy on biomarkers and virus specific antibody responses are defined as follows:

    - Population: Participants with CHB on stable NA therapy; For the time to ALT normalisation variable, population will be aforementioned participants with baseline ALT >ULN.
    - Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy
    - Intercurrent Events: Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be ignored (treatment policy). PegIFN ineligibility will be ignored (treatment policy); Rescue medication will be ignored (treatment policy), except for ALT normalisation which can only be achieved in the absence

of rescue medication; Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be ignored (treatment policy strategy).

- Categorical Variables:
    - Achieving HBsAg <LLOQ and HBV DNA <LLOQ at two time points: (1) the planned end of treatment and (2) at the end of 24 weeks follow-up
    - Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL).
    - ALT normalisation (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN
    - HBe antibody (anti-HBeAg) levels
- Population summary of Categorical Variables: percentage of participants in each category for each treatment arm
- Continuous Variables:
    - Actual values and change from baseline over time of HBsAg, HBV DNA, and HBeAg levels
    - Actual values and change from baseline over time for HBs antibody (anti-HBsAg) levels over time
    - Actual values and change from baseline over time for ALT.
- Population summary of Continuous Variables: mean values and mean changes from baseline of each variable for participants in each treatment arm
- Time to Event Variable:
    - Time to ALT normalisation in absence of rescue medication in participants with baseline ALT>ULN
- Population summary of Time to Event Variable: Turnbull's estimator for non-parametric estimation of Time to ALT normalisation in each treatment arm

The estimands supporting this objective are the population summary for each variable in each treatment arm in the population regardless of discontinuation of, interruption in, or non-adherence to planned treatment, and regardless of rescue medication (except for ALT normalisation which can only be achieved in the absence of rescue medication) or PegIFN ineligibility.

Missing data for variables defined above will be ignored, only available data will be summarised. Further details will be provided in the report and analysis plan (RAP).

2. Estimands supporting secondary objective of investigating the durability of virological response after sequential therapy with 12 weeks of GSK3228836 followed by up to 24 weeks of PegIFN in participants with CHB on stable NA therapy for up to 36 weeks

off treatment are defined the same as the above secondary estimand, focusing on the timepoints following the 24 weeks off-treatment period.

3. Estimands supporting secondary objective of comparing efficacy between treatment arms of 12 and 24 weeks of GSK3228836 followed by up to 24 weeks of PegIFN are defined as follows:

   - Population: Participants with CHB on stable NA therapy
   - Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy. One treatment comparison between Arms 1 and 2 up to 24 weeks off-treatment
   - Categorical Variables:
     - Achieving SVR (HBsAg <LLOQ and HBV DNA <LLOQ) at the planned end of sequential treatment and over the 24 weeks follow-up.
     - Population Summary of Categorical Variables: difference in percentage of participants who achieve SVR between treatment arms.

   - Intercurrent Events: Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be ignored (treatment policy). PegIFN ineligibility will be ignored (treatment policy); Participants who have used rescue medication will be counted as non-responders (composite strategy); Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled assuming they had not happened (hypothetical strategy).

The estimands supporting this objective in participants with CHB on stable NA therapy for the treatment comparison is the difference between treatment arms 1 and 2 in the proportion of participants that achieve SVR for 24 weeks after the planned end of sequential treatment, in the absence of rescue medication, regardless of ineligibility to receive PegIFN, regardless of discontinuation of, interruptions in or non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events.

9.4.3.2. Handling of withdrawal from study and missing data for secondary endpoints

9.4.3.2.1. Comparison of efficacy between treatment arms

Two approaches will be used to determine a participant's response when HBsAg and HBV DNA data are missing from visits required to derive the secondary estimand of comparing efficacy between treatment of 12 and 24 weeks of GSK3228836 followed by up to 24 weeks of PegIFN

1) For participants where wide disruptive events (such as COVID-19 pandemic) prevent assessment of the HBsAg and HBV DNA required to derive SVR, SVR will be imputed using all available data for participants for whom SVR can be assessed. For other participants where SVR in the absence of rescue medication cannot be ascertained due to missing data (withdrawal from the study or missing due to other reasons, but not due to a

wide disruptive event), the participant will be assumed not to have achieved SVR (non-responder imputation).

2) For the estimand supporting the objective of comparing efficacy between treatment arms, a sensitivity analysis will be performed using the Bayesian model described in Section 9.4.3.3 assuming missing at random whereby a participant's response will be imputed using all available data (on and off treatment values) for participants who completed the study.

9.4.3.2.2. Other secondary endpoints

Other than the HBsAg and HBV DNA data supporting the secondary objective of comparing efficacy between treatment arms, missing data for variables defined in any other secondary or exploratory estimand will be ignored, assuming missing completely at random.

9.4.3.3. Secondary Efficacy Analyses

The secondary efficacy comparison of interest is the difference in sustained virologic RR for 24 weeks after the planned end of sequential treatment between treatment arms:

- Arm 1 vs. Arm 2 in percentage of participants achieving SVR for 24 weeks after the planned end of sequential treatment, without use of any rescue medication.

The model in Section 9.4.2.4 will be used to separately estimate the log odds of response for each treatment arm. Comparisons between the treatment arms will be conducted by taking difference of log odds. The point estimates of differences in sustained virologic RR with 95% credible intervals will be calculated for the treatment comparisons described in the estimands. Handling of withdrawal from study and missing HBsAg and HBV DNA data is described in Section 9.4.3.2. Details of the model will be included in the RAP.

9.4.4. Safety Endpoints

All safety analyses will be based on the Safety Population.

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

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

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

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

9.4.5. Exploratory Endpoints

CCI

[redacted]

9.4.5.1. PK and PK-PD Analyses

Pharmacokinetics (PK) of GSK3228836 and PegIFN will be characterised. In all participants, Cτ and terminal half-life (t½) will be estimated, as data permit.

PK-PD relationships including PK-efficacy relationships and PK-safety relationships will be evaluated, as data permit:

- Efficacy assessments for PK/PD relationship include but not limited to:
  - Categorical: virologic response, seroclearance (HBsAg <LLOQ, HBV DNA <LLOQ), and seroconversion (anti-HBsAg and anti-HBeAg);
  - Change from baseline: HBsAg, HBV DNA, anti-HBsAg and anti-HBeAg levels;
  - Time to event: virologic response (HBsAg and HBV DNA levels < LLOQ), nadir of HBsAg and HBV DNA, HBsAg<LLOQ, HBV DNA <LLOQ, seroconversion (anti-HBsAg and anti-HBeAg), peak of ALT flares
- Safety assessments for PK/PD relationship include but not limited to vital signs, laboratory measurements and adverse events
- PK assessments include but not limited to Cτ and terminal half-life (t½).

9.4.5.2. Safety and Tolerability

The safety profile of sequential therapy with GSK3228836 (up to 24 weeks) followed by PegIFN (up to 24 weeks) in participants with CHB on stable NA therapy will be investigated.

- Clinical assessments include laboratory measurements and adverse events at timepoints specified in the SoA.

CCI

[redacted]

9.4.5.5. Biomarkers

The effect of GSK3228836 and PegIFN sequential therapy on immunological biomarkers will be assessed. The relationship(s) between virology biomarkers including HBsAg and immunological biomarkers will be described.

- Biomarker assessments include Laboratory measurements of and correlation between the following:
  - Virological biomarkers, including specific viral parameters (HBeAg, HBV DNA, HBV RNA, HBcrAg)
  - Soluble biomarkers, including levels of circulating cytokines and chemokines
  - Markers of immune cell function, including relative frequencies of immune cell subsets among PBMCs, activation status as determined by phenotyping and gene expression patterns, and functional assays including HBV-specific cytokine and/or antibody production

Timepoints are specified in the SoA.

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

9.5. Interim Analysis

One interim analysis is planned for the study in addition to regular IDMC safety reviews (see Section 10.1.5). The interim analysis will be based on the ITT population.

The approximate timing, endpoint and criteria for the interim analysis is summarised in Table 16.

Table 16 Interim Analysis Timing, Endpoint and Decision Rule

Interim	Timing	Endpoint	Decision Rule
1	All participants complete end-of-treatment visit	Sustained virologic response rate (primary endpoint)	The predicted end-of-study sustained virologic response rate will be modelled to support development plan decision making. No option to stop the trial at this point as all participants will have completed treatment.

The RAP will describe the planned interim analysis in greater detail.

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 International Conference on Harmonisation (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/IEC
  - 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 their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised 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 requirements, where applicable, and the IRB/IEC or study centre.
- 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 authorised 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 their legally authorised 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. Where approved by the IRB/IEC, the investigator or authorised designee will inform each participant of the possibility of further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of

disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised 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:

- 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.
- Determining the type of information needed for review of efficacy/safety data, as required, in the context of benefit/risk.
- Recommending the format for the presentation of this information.
- Reviewing data collection methods, safety/efficacy monitoring procedures and making recommendations for additions or adjustments to the trial design following interim analysis.

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

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are 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 anonymised 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.
- 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 summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations [CRO]).
- 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.

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 authorised 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.

Study/Site Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- 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 CRO(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 multicentre 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 17 will be performed by the central laboratory.

Local laboratory results are required for analysis of platelets during the GSK3228836 dosing period. The blood draw can be taken the day before GSK3228836 dosing. Results must be available 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. Pregnancy testing (urine or serum as required by local regulations) should be conducted according to the Schedule of Assessments (Section 1.3) during the study. 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 participation in the study.

Table 17 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count[1] RBC Count Haemoglobin Haematocrit	RBC Indices: mean corpuscular volume mean corpuscular haemoglobin	WBC count (with Differential if WBC abnormal): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase / Serum Glutamic-Oxaloacetic Transaminase	Total, indirect and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase/ Serum Glutamic-Pyruvic Transaminase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• By dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
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 oestradiol (as needed only) • Serology (HIV antibody, hepatitis C virus antibody, and hepatitis D virus antibody) • Hepatitis B serology (HBsAg, anti-HBsAg, anti-HBeAg, HBV DNA, HBV RNA, HBcrAg) • Other laboratory: TSH/T4, prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), Alpha-fetoprotein, ANCA (MPO-ANCA, PR3-ANCA), APRI/Fibrosure, Complement factors C3, C4, C5a, and Bb, hs-CRP, MCP-1, angiopoietin II, PBMC, soluble protein, PAX Gene • Urine ACR • Optional collections: 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

Additional tests listed under safety follow-up processes	**Liver Chemistry Stopping Criteria[3]**
	• 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
	• PK sample
	• Serum CPK 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 HPLC assay

	Drug Induced Vascular Inflammation and Complement Stopping Criteria • CH50 • Factor B level • Factor H level • sC5b-9

Laboratory Assessments	Parameters
	Haematological 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] • SPEP/ UPEP • complement panel (C3, C4, C5a and Bb)

NOTES:
1. Platelets will require local/central lab collection while participants are GSK3228836 on-treatment. The blood draw can be taken the day before GSK3228836 dosing. Results must be available prior to dosing.
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 normalised 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 unfavourable 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/ legally acceptable representative (LAR(s)) 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/LAR(s) 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 /LAR's 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/LAR(s) will be collected during interview with the participants/ LAR(s) 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 <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, 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 or part 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 fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening

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

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation 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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

- Hospitalisation 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, diarrhoea, 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. Other situations:

- 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 jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of 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
- Revascularisation

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study 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 utilised 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 recognised 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.
- 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 or the SAE coordinator.
- 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 SRM.

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-oestrogen 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 sterilisation 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.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

- 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.

- Postmenopausal female

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

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

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
Intrauterine device
Intrauterine hormone-releasing system [b]
Bilateral tubal occlusion
Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.)
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
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 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 amenorrhea method are not acceptable methods of contraception. e. Male condom and female condom should not be used together (due to risk of failure from friction).

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 foetal 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 chronic hepatitis B 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 may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed 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 chronic hepatitis B 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.

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 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 SRM.
  - CPK and 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 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 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 computerised 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.

GSK3228836 rechallenge after stopping criteria are met (i.e., study treatment discontinued) by any participant in this study is not allowed.

GSK3228836 restart may be considered only for liver events as follows:

Restart Following Transient Resolving Liver Stopping Events Not Related to GSK3228836

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 <3 x ULN).
  - 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.
  - IRB/IEC approval of study intervention restart, if required, has been obtained.

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

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

10.7. Appendix 7: Country-specific requirements

10.7.1. China

The following sections outline China-specific changes from the main protocol. In China, collection of exploratory/biomarker labs will be contingent on agreements with China regulatory, Human Genetics Resources Administration of China (HGRAC).

10.7.1.1. China Schedule of Activities

The SoA in China will be completed as per Section 1.3, however collection of the following laboratory assessments will be contingent on agreements with CHINA regulatory (HGRAC) and will be optional for Chinese participants:

- PBMC Collection for immunophenotyping
- Soluble Protein (Immunology)
- PAXGene RNA for expression analysis in whole blood

10.7.1.2. China Biomarkers and Archived Samples

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

CCI

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

- For China-stored samples (e.g., archived samples) may be used for the purposes of follow-up exploration of laboratory findings and/or AEs (e.g., see Section 7 for additional analyses in case of an AE or SAE).

10.8. Appendix 8: Abbreviations and Trademarks

ACR	albumin to creatinine ratio
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
cANCA	classical anti-neutrophil cytoplasmic antibodies
pANCA	perinuclear anti-neutrophil cytoplasmic antibodies
APRI	aspartate aminotransferase-platelet index
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
BDI-II	Beck Depression Inventory-II
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
Ct	concentration
CNS	central nervous system
COVID-19	Corona Virus Disease-19
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organisation
C-SSRS	Columbia Suicide-Severity Rating Scale
CV	cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
DIVI	drug induced vascular inflammation
DILI	drug induced liver injury
dL	decilitres
DNA	deoxyribonucleic acid
dsDNA	double stranded deoxyribonucleic acid
eCRF	electronic case report form
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
eGFR	Estimated glomerular filtration rate
GSK	GlaxoSmithKline
HBcrAg	hepatitis B core-related antigen
Anti-HBeAg	hepatitis B virus e-antigen antibody
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
HGRAC	human Genetics Resources Administration of China
HIV	human immunodeficiency virus
HPF	high-power field
HPLC	high performance liquid chromatography
HRT	hormonal replacement therapy

hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IDO	indoleamine 2,3 dioxygenase
IEC	Independent Ethics Committee
IFN	Interferon
IMP	investigational medicinal product
INR	international normalised ratio
IP	investigational product
IRB	Institutional Review Board
ISR	injection site reaction
IVRS/IWRS	Interactive Voice/Web Response System
ITT	Intent-to-Treat
IU	international units
IP	Investigational Product
Kg	kilograms
kPa	kilopascals
L	litres
LAR(s)	Legally acceptable representative
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification
m^2	square meters
MCP	monocyte chemoattractant protein
mEq	milliequivalents
mcg	microgram
mg	milligrams
Min	minutes
mL	millilitres
mm^3	cubic millimetres
MOE	methoxyethyl
msec	milliseconds
MSDS	Material Safety Data Sheet
NA	nucleos(t)ide analogue
Ng	nanograms
Nucleos(t)ide	nucleoside or nucleotide
OAT	organic anion transporter
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics(s)
PEG	pegylated
PegIFN	peginterferon
PK	pharmacokinetic(s)
POC	proof of concept
PT	prothrombin time
QTcF	Fridericia's QT correction formula
QTLs	quality tolerance limits
RAP	reporting and Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
RNAse H	Ribonuclease H
mRNA	Messenger RNA
RPGN	rapidly progressive glomerulonephritis

RR	response rate
SAE	serious adverse event
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
SoA	Schedule of Activities
SPEP	serum protein electrophoresis
SRM	Study Reference Manual
SRT	Safety Review Team
SVR	Sustained Virologic Response
t½	terminal half-life
TCM	traditional Chinese medicine
TSH	thyroid stimulating hormone
U	units
UA	urinalysis
µg	micrograms
ULN	upper limit of normal
UPEP	urine protein electrophoresis
mol	micromole
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	woman of non-childbearing potential

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