TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Dose and Multiple Doses of GSK3389404 in Chronic Hepatitis B Subjects

Compound Number: GSK3389404

Development Phase: IIA

Effective Date: 13-JUN-2018

Protocol Amendment Number: 06

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N277028_00	2016-JUN-21	Original
2016N277028_01	2017-FEB-21	Amendment No. 1
Reasons for the Amendment: To update the subject population in Part 2 from treatment naïve to treatment experienced. To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg. To reduce complexity and visit burden for subjects. To make minor edits for clarity.		
2016N277028_02	2017-MAR-03	Amendment No. 2
Reasons for the Amendment: To include patients with ALT less than 5x upper limit of normal. To make minor edits for clarity. [Rationale: see Appendix 7]		
2016N277028_03	2017-MAR-07	Republishing
Reasons for the Republishing: Protocol title of the published amendment did not match the original (2016-JUN-21) protocol title and was corrected.		
2016N277028_04	2017-JUN-28	Amendment No. 3
Reasons for the Amendment: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1. To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. To remove the requirement for a minimum viral load at entry for treatment naïve subjects or subjects that have had prior treatment with interferon or nucleosides in Part 1. To update the subject population in Parts 1 and 2 to include women of child bearing potential. To update the subject population in Parts 1 and 2 to include patients with GFR ≥60 mL/min after consultation with the GSK medical monitor. To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study. To reduce complexity and visit burden for subjects. To provide information from the results of the GSK3389404 first-in-human study 202007. To provide corrections to the statistical simulations. To provide minor edits for clarity and typographical errors.		
2016N277028_05	2017-OCT-21	Amendment No. 4
To remove females of reproductive potential for Part 1 of study 205670 based on feedback from South Korea MFDS. To provide edits for clarity.		

2016N277028_06	2018-MAR-06	Amendment No. 5
To update the protocol to include the treatments for Part 2. To include an optional additional 9 month off-treatment follow up period. To provide updates to the pre-clinical and clinical data. To include management review of un-blinded data. To provide updates to the statistical sections. To provide edits for clarity.		
2016N277028_07	2018-JUN-05	Amendment No. 6
To correct the planned study duration for subjects. To allow inclusion of subjects with ALT ≤ 2xULN. To add greater clarity for exclusions 4, 8g, 9, and 11. To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study. To update the Time and EventsTable for the optional follow-up period. To update the unblinded senior management review. To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period). To make minor edits for clarity		
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Reasons for the Republishing: To clarify exclusion criteria 13.		

SPONSOR SIGNATORY

PPD

13 June 2018

Dickens Theodore, MD
Senior Director, Clinical Development,
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Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205670

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	
Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 205670

Rationale

This is a Phase IIa, 2-part study examining the first administration of GSK3389404 in subjects with chronic hepatitis B (CHB). This study will evaluate safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of GSK3389404 and aim to establish proof-of-mechanism. Part 1 will assess the safety, tolerability, PK, and PD profiles of single ascending subcutaneous (SC) doses of GSK3389404. Part 2 will assess the safety, tolerability, PK, and PD profiles of multiple doses of GSK3389404. In addition, Part 2 will provide an initial evaluation of efficacious dose levels and dosing regimens. Finally, this study may provide an initial evaluation of any differences in PD between hepatitis B virus (HBV) e-antigen (HBeAg)-positive and HBeAg-negative subjects with CHB. Data from this study will support subsequent studies by providing an early assessment of safety and PD in the target patient population.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To assess the safety, tolerability, and PK profile of GSK3389404 in single (Part 1) and multiple (Part 2) administration in subjects with CHB.	**Safety and Tolerability** As measured by clinical assessments including, but not limited to • Vital signs • Physical examinations • 12-lead electrocardiograms (ECGs) • Laboratory measurements (e.g., chemistry, hematology) • Adverse events **Pharmacokinetic Profile:** Derived GSK3389404 plasma PK parameters including, but not limited to area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), time of maximum observed concentration (t_{max}), terminal half-life ($t_{½}$) and apparent subcutaneous plasma clearance (CL/F)
To identify one or more efficacious dose(s) and dosing regimen(s) of GSK3389404 over a planned duration of 3 months (Part 2).	**Efficacy** Response rate (RR) based on the proportion of subjects with at least a 1.5 times log 10 IU/mL reduction of hepatitis B surface antigen (HBsAg) levels from baseline anytime during the study.
Secondary	
To assess the PD effect of GSK3389404 in subjects with CHB (Part 1 and Part 2).	Correlation between GSK3389404 PK parameters and PD parameters, including hepatitis B virus (HBV) deoxyribonucleic acid (DNA) as appropriate, HBsAg, and HBeAg levels (as appropriate, HBeAg-positive subjects).
To investigate the PK of the metabolite of GSK3389404, also known as ISIS 505358,	Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

Objectives	Endpoints
following single and multiple dose administration of GSK3389404 (Part 1 and Part 2).	
Exploratory	
To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (Part 1 and Part 2, if applicable).	Correlation between PD parameters, including HBV DNA, HBV RNA, HBsAg, and/or hepatitis B core-related antigen (HBcrAg).
To describe the seroconversion of subjects, defined as presence of HBV surface antibody (HBsAb) (Part 2 only).	Rate of seroconversion.

Overall Design

This is a Phase IIa, multicenter, randomized, double-blind (sponsor un-blinded in Part 1), placebo-controlled, 2-part study to the assess safety, tolerability, PK, and PD profiles of GSK3389404 in subjects with CHB.

Part 1 plans to enroll subjects primarily from the Asia-Pacific region (including, but not limited to, Hong Kong, South Korea, and Taiwan). Part 1 will be conducted as a single ascending dose (SAD) study with up to 5 planned cohorts.

- Cohort A (HBeAg-positive and/or HBeAg –negative subjects): GSK3389404 30 mg SC or placebo
- Cohort B (HBeAg-positive and/or HBeAg –negative subjects): GSK3389404 60 mg SC or placebo
- Cohort C (HBeAg-positive and/or HBeAg –negative subjects): GSK3389404 120 mg SC or placebo
- Cohort C1, optional (HBeAg-positive or HBeAg-negative subjects): GSK3389404 120 mg SC or placebo
- Cohort D (HBeAg-positive and/or HBeAg –negative subjects): GSK3389404 ≤240 mg SC or placebo

Within each cohort, subjects will be randomized to receive GSK3389404 or placebo SC in a 3:1 ratio. Cohorts A, B, C, C1, and D will be conducted in a sequential fashion; Cohort C1 is an optional cohort that may be dosed after Cohort C or in parallel with Cohort D. Dose Escalation Committee meetings will be held between sequential cohorts. The decision to enroll the optional Cohort C1 will be made at a prior Dose Escalation Committee Meeting.

Part 2 will be conducted as a multiple-dose, dose-ranging study. Part 2 plans to enroll subjects primarily from the Asia-Pacific region, including Japan. Japan may also participate in an optional Japanese Part 2 sub-study. Subjects will be randomized to different parallel dose levels and regimens or placebo. The dose levels and regimens for Part 2 will be selected after review of safety (at a minimum of adverse events [AEs], laboratory chemistry, hematology, and electrocardiogram [ECG]), PK, and PD data from Part 1 (through Day 3). The treatments that were selected for Part 2 based on data from

Part 1 are 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo.

In Part 2, safety data from a sentinel group (1 subject from each active treatment group and the corresponding matching placebo) will be reviewed by the GlaxoSmithKline (GSK) internal clinical team or Safety Review Team (SRT) in a blinded manner. Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure in the sentinel group. Safety data from all subjects will be reviewed by the GSK internal clinical team or SRT in a blinded manner on a regular basis thereafter.

Details of the optional Japanese Part 2 sub-study will be detailed in a Japan country-specific amendment/supplement.

Since this is the first administration of GSK3389404 in subjects with CHB, the study design may change based on emerging data (safety, tolerability, and PD) from each cohort and/or part.

Treatment Arms and Duration

In Part 1, five dosing cohorts are planned and the total study duration, including screening, treatment, and post-treatment follow-up, is not expected to exceed 13 weeks for each subject.

- A 30-day screening window is planned
  - Eligible subjects who fall within a 45-day window (15 days exceeding the 30-day screening window) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility.
- Dosing will take place on Day 1 with post-treatment follow-up on Day 3.
  - Based on subject and study site preference, subjects have the option to be domiciled at the study site or present to the study site as outpatients.
    - Admission to the study site is optional from Day -1 to Day 2.
    - Subjects admitted to the study site may be discharged on Day 1, Day 2, or Day 3, based on subject and study site preference.
    - Subjects may present as outpatients on Day 1 and/or Day 3, based on subject and study site preference.
  - On Day 1, the SC dose will be administered per cohort assignment (Cohort A, B, C, C1, or D) and randomized treatment assignment (GSK3389404 or placebo).
- A post-treatment follow-up period is planned where subjects will present for study visits on Days 3, 8, 15, 22, 30, and 60.

In Part 2, 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo are planned and the total study duration, including

screening, dosing, and post-treatment follow-up, is not expected to exceed 71 weeks for each subject.

- A 30-day screening window is planned
  - Eligible subjects who fall within a 45-day window (15 days exceeding the 30-day screening window) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility.
- An expected study treatment exposure of up to 85 days is planned where subjects will receive multiple SC doses of 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo.
  - A sentinel group (1 subject from each active treatment group and the corresponding matching placebo) will be dosed first.
    - Subjects enrolled in the sentinel group will be dosed and followed (per the Time and Events Tables). Safety data from all subjects in the sentinel group will be reviewed (must be at least 2 weeks of exposure, but may include more data).
  - Randomization for the remaining subjects will continue after the safety data from all subjects in the sentinel group are reviewed.
  - For all regimens, subjects will present for weekly study visits through Day 85 with dosing days as follows:
    - For once weekly dosing, subjects will be administered GSK3389404 or placebo as a SC dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.
    - For bi-weekly (every 2 weeks) dosing, subjects will be administered GSK3389404 or placebo as a SC dose on Days 1, 15, 29, 43, 57, and 71.
- A protocol mandated post-treatment follow-up period is planned where subjects will present for study visits on Days 85, 92, 99, 113, 141, and 169.
- An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.

Type and Number of Subjects

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects, and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAg-negative subjects (or none at all). For Part 2, HBeAg-positive and/or HBeAg-negative subjects will be enrolled.

Approximately 73 subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, twelve subjects were enrolled. Originally, approximately 20 to 40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol.
- In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. There are approximately 11 subjects in each of the active treatment groups and approximately 6 subjects in the placebo group.
- If Japan participates in the optional Japanese Part 2 sub-study, approximately 22 subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement.

Analysis

Part 1 and Part 2

Safety and tolerability parameters (AEs/serious AEs [SAEs], physical exams, vital signs, 12-lead ECGs, and clinical laboratory measurements) will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular or graphical formats, as appropriate.

GSK3389404 and ISIS 505358 plasma concentration-time data will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular and graphical formats. GSK3389404 and ISIS 505358 (parent compound) PK parameters, including but not limited to area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose (AUC_{dose}) to 24 hours post-dose (AUC_{∞})), C_{max}, t_{max}, $t_{½}$, and CL/F (GSK3389404 only), will be listed by subject and summarized by treatment group and HBeAg status.

Pharmacodynamic data (HBsAg, HBeAg, and HBV DNA) will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular and graphical formats, as appropriate. Correlations between PD data in HBeAg-positive and HBeAg-negative subjects will be explored graphically. Correlation between PK parameters and PD parameters will be explored graphically.

Part 2

The primary efficacy objective is to select the efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint, response rate (RR), based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least a 1.5 times log 10 IU/mL reduction of HBsAg levels from baseline anytime during the study. A model based probability inference approach in Bayesian framework will be used for decision-making as the primary efficacy analysis. An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 90%), i.e., $P(RR_{ACT} > RR_{PBO}) \geq 90\%$, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

A supportive analysis will also be performed using pair-wise comparison in Bayesian framework using the same criteria as mentioned above.

Dose response curve for each treatment group will be estimated to determine the dose response of the particular treatment group. Further details will be provided in the Reporting and Analysis Plan (RAP).

The RR in each of the treatment groups will also be summarized in frequentist approach by descriptive measures including 90% confidence intervals using exact method.

2. INTRODUCTION

GSK3389404 is being developed for the treatment of chronic hepatitis B (CHB) virus infection. The development goal for GSK3389404 is the establishment of a finite duration treatment that results in sustained suppression of hepatitis B virus (HBV) replication and viral antigen production after cessation of all treatments for CHB due to the restoration of a functional immune response in the absence of high antigen levels.

ISIS 505358, known as the parent molecule of GSK3389404, is a 2′-O-(2′-methoxyethyl) (2′-MOE) chimeric second-generation antisense oligonucleotide (ASO) drug targeted to HBV ribonucleic acid (RNA). GSK3389404, the prodrug, was derived from ISIS 505358. GSK3389404 is a 2′-MOE chimeric second-generation ASO drug targeted to HBV RNA that is covalently bonded to triantennary N-acetyl galactosamine (GalNAc), a high affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO GalNAc- conjugate to enhance delivery of GSK3389404 to hepatocytes.

Following entry into target cells the GalNAc conjugate prodrug GSK3389404 is metabolized within hepatocytes to release ISIS 505358. ISIS 505358 is complementary to sequences present in all HBV-derived RNA transcripts and its hybridization (binding) 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.

ISIS 505358 has been studied in healthy volunteers at various dose levels and for durations up to 1 month. GSK3389404 has been administered to healthy volunteers in Study 202007, a recently completed study to assess the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses of GSK3389404. Results from the completed study of ISIS 505358 and from the single ascending dose (SAD) portion of Study 202007 have not identified any safety findings to date that would preclude further clinical development. A comprehensive summary of the preclinical findings for GSK3389404 including pharmacology, drug metabolism and pharmacokinetics (DMPK) and toxicology are available in the Investigator's Brochure (IB). The clinical safety findings for both GSK3389404 and ISIS 505358 are also summarized in the IB [GlaxoSmithKline Document Number 2015N236049_04].

2.1. Study Rationale

This is a Phase IIa, 2-part study examining the first administration of GSK3389404 in subjects with CHB. This study will evaluate the safety, tolerability, PK, and pharmacodynamic (PD) profile of GSK3389404 and aim to establish proof-of-mechanism. Part 1 will assess the safety, tolerability, PK and PD profiles of single ascending subcutaneous (SC) doses of GSK3389404. Part 2 will assess the safety, tolerability, PK and PD profiles of multiple doses of GSK3389404. In addition, Part 2 will provide an initial evaluation of efficacious dose levels and dosing regimens. Finally, this study may provide an initial evaluation of any differences in PD between HBV e-antigen (HBeAg)-positive and HBeAg-negative subjects with CHB. Data from

this study will thus support subsequent clinical studies by providing an early assessment of safety and PD in the target patient population.

2.2. Brief Background

Infection with HBV, especially chronic infection, is a significant worldwide medical problem. More than 2 billion of the world's population has been infected. Of these, an estimated 240 million are chronically infected [WHO, 2015]. Every year, 650,000 people die from HBV-related disease complications. For those with chronic infection, 20 to 30% progress to liver cirrhosis or hepatocellular carcinoma (HCC) [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, HCC, and death. This goal can be achieved if HBV replication is suppressed in a sustained manner thereby decreasing the histological activity of CHB and reducing the risk of cirrhosis and HCC [Liaw, 2004; Feld, 2009]. In both HBeAg-positive and HBeAg-negative CHB, the ultimate treatment endpoint is loss of detectable serum hepatitis B surface antigen (HBsAg) [Lok, 2009; EASL, 2012]. Loss of HBsAg is preceded by a robust immunological response to HBV infection resulting in sustained suppression of serum HBV deoxyribonucleic acid (DNA) and disease resolution.

First-line therapy for CHB is treatment with a nucleoside or nucleotide (nucleos(t)ide) analogue. At least 6 nucleos(t)ide analogues are available for the treatment of CHB patients [Lok, 2009; EASL, 2012]. While these antiviral agents are effective in suppressing HBV replication in both HBeAg-positive and HBeAg-negative CHB, patients frequently relapse after treatment is discontinued, particularly if HBsAg loss was not achieved. Treatment with a pegylated interferon (PEG-interferon) is also approved for CHB [Lok, 2009; EASL, 2012] for a defined treatment duration (usually up to 48 weeks). Because of their frequent and sometimes severe side effects and high cost versus a small gain in treatment response, PEG-interferons are less frequently used than nucleos(t)ide analogues. Unfortunately, with both the nucleos(t)ides and PEG-interferon, HBsAg loss and the subsequent development of antibodies to HBsAg is rarely achieved. Rates of HBsAg loss following 12 months of treatment with either a nucleos(t)ide or PEG-interferon generally range from 0 to 3% in most studies [Lok, 2009; EASL, 2012]. Loss of HBeAg occurs more frequently following treatment with either the nucleos(t)ides or PEG-interferon, approximately 15 to 30% after 1 to 2 years of therapy, but off treatment durability is variable and questions remain as to whether virologic responses can be maintained over an extended follow-up period. Thus, the majority of patients on treatment fail to achieve a sustained off-treatment virological- response and require extended and often life-long therapy to suppress HBV DNA.

The continued production of viral antigens by infected hepatocytes is thought to interfere with immune clearance of both the infected cells and circulating virus particles [Vanlandschoot, 2003]. In vitro studies with human peripheral blood mononuclear cells (PBMCs) have shown HBsAg impairs the functioning of dendritic cells and inhibits the activation of monocytes [Vanlandschoot, 2002; Op den Brouw, 2009]. Further, data suggest the production of vast excess of non-replication competent HBsAg (so called "sub-viral particles") likely functions as a decoy for host antibody responses. Most

chronically infected patients produce antibody to HBsAg, but these can only be detected as immune complexes due to the vast excess of circulating antigen [Maruyama, 1993]. HBeAg is also thought to have a role in immune response evasion through down-regulation of the innate immune system [Milich, 1998; Wu, 2009; Walsh, 2012]. As noted above, loss of HBsAg expression is rarely achieved while loss of HBeAg expression occurs in a higher proportion of patients. It is believed that HBsAg may be the main antagonist of immune clearance.

Should 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]. 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. GSK3389404, an antisense inhibitor, was designed to inhibit the synthesis of HBsAg without having a direct effect on covalently closed circular DNA or integrated HBV DNA. GSK3389404 is not an immune modulator. Therefore, GSK3389404 treatment permits examination of whether reduction of HBsAg allows resumption of a host immune response against HBV and infected cells and can induce HBsAg seroclearance.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety, tolerability, and PK profile of GSK3389404 in single (Part 1) and multiple (Part 2) administration in subjects with CHB.	**Safety and Tolerability** As measured by clinical assessments including, but not limited to the following: • Vital signs • Physical examinations • 12-lead electrocardiograms (ECGs) • Laboratory measurements (e.g., chemistry, hematology) • Adverse events **Pharmacokinetic Profile:** Derived GSK3389404 plasma PK parameters including, but not limited to area under the concentration-time curve (AUC), maximum observed concentration (C_{max}, time of maximum observed concentration (t_{max}, terminal half-life ($t_{½}$, and apparent subcutaneous plasma clearance (CL/F).
To identify one or more efficacious dose(s) and dosing regimen(s) of GSK3389404 over a planned duration of 3 months (Part 2).	**Efficacy** Response rate (RR) based on the proportion of subjects with at least a 1.5 times log 10 IU/mL reduction of HBsAg levels from baseline anytime during the study.
Secondary	
To assess the PD effect of GSK3389404 in subjects with CHB (Part 1 and Part 2).	Correlation between GSK3389404 PK parameters and PD parameters, including HBV DNA as

Objectives	Endpoints
	appropriate, HBsAg, and HBeAg levels (as appropriate, HBeAg-positive subjects).
To investigate the PK of the metabolite of GSK3389404, also known as ISIS 505358, following single and multiple dose administration of GSK3389404 (Part 1 and Part 2).	Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.
Exploratory	
To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (Part 1 and Part 2, if applicable).	Correlation between PD parameters, including HBV DNA, HBV RNA, HBsAg, and/or hepatitis B core-related antigen (HBcrAg).
To describe the seroconversion of subjects, defined as presence of HBV surface antibody (HBsAb) (Part 2 only).	Rate of seroconversion.

4. STUDY DESIGN

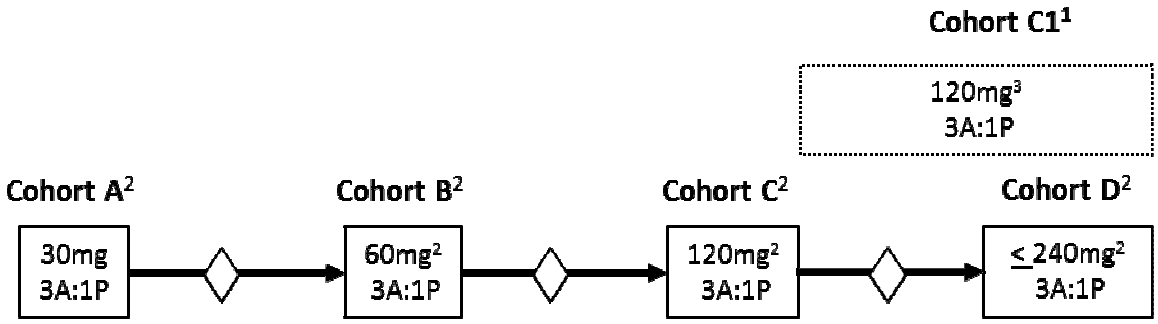
4.1. Overall Design

This is a Phase IIa, multicenter, randomized, double-blind (sponsor un-blinded in Part 1), placebo-controlled 2-part study to assess the safety, tolerability, PK, and PD profiles of GSK3389404 in subjects with CHB.

Part 1 plans to enroll subjects primarily from the Asia-Pacific region (including, but not limited to, Hong Kong, South Korea, and Taiwan). Part 1 will be conducted as a SAD study with 5 planned cohorts ranging from 30 mg to a maximum of 240 mg GSK3389404 (Figure 1). Within each cohort, subjects will be randomized to receive GSK3389404 or placebo in a 3:1 ratio. Cohorts A, B, C, C1, and D will be conducted in a sequential fashion. Cohort C1 is an optional cohort that may be dosed after Cohort C or in parallel with Cohort D. The decision to enroll the optional Cohort C1 will be made at a prior Dose Escalation Committee Meeting. Dosing in each cohort is contingent on the safety, PK, and PD profiles of at least 3 subjects who received GSK3389404 at the previous dose level. Dose escalation can only occur after the Dose Escalation Committee (Section 10.8.1), consisting of the principal investigator, medical monitor, GSK study team leader, pharmacokineticist, GSK Global Clinical Safety and Pharmacovigilance [GCSP] representative, GSK data manager, programmer, and statistician (or appropriate designees) have reviewed the available safety, tolerability, PK, and PD results for the previous cohort and finds the safety profile through Day 3 supportive to proceed with the evaluation of the next higher dose level. Dose escalations and/or reductions will progress with modifications based on the actual human safety and PK data from the preceding cohort(s). Cohorts may be expanded (additional subjects may be enrolled) to further evaluate safety, PK, and/or PD findings at a given dose level. Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Section 6.3 provides additional information on planned dose adjustments.

Study treatment and post-treatment follow-up Time and Events Tables are provided in Section 7.1.

Figure 1 Part 1: Single Ascending Dose, Study Design Schematic



A = active (GSK3389404); HBeAg = hepatitis B virus e-antigen; P = placebo.
◊ = Dose EscalationCommittee meeting

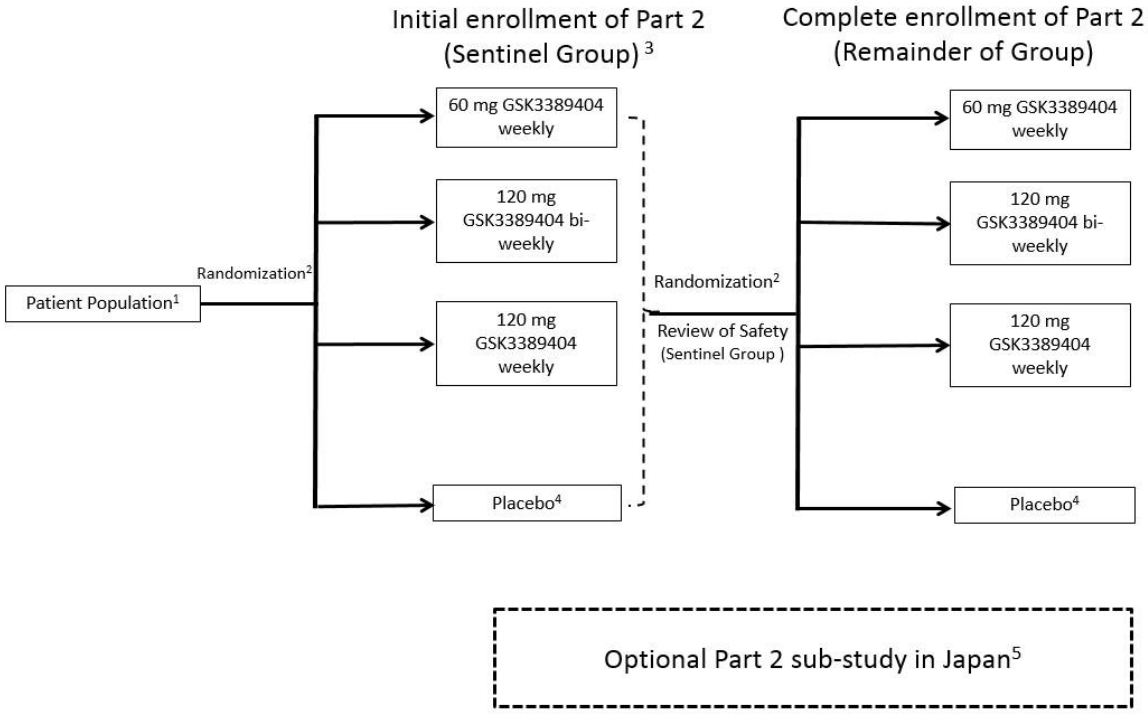
1. Cohort C1 may include HBeAg-positive or HBeAg-negative subjects and, if enrolled, may be dosed after Cohort C, in parallel with Cohort D (optional).
2. HBeAg-positive and/or HBeAg-negative subjects will be enrolled in these cohorts.
3. Dose escalations and/or reductions will progress with modifications based on the actual human safety and PK data from the preceding cohort(s). Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Dose will not exceed 240 mg.

Part 2 will be conducted as a multiple-dose, dose-ranging study (Figure 2). Part 2 plans to enroll subjects primarily from the Asia-Pacific region, including Japan. Japan may also participate in an optional Japanese Part 2 sub-study. Subjects will be randomized to different parallel dose levels and regimens or placebo. A sentinel group will be dosed first and a safety review conducted before the remainder of subjects are dosed. The dose levels and regimens for Part 2 have been selected after Part 1 safety, (at a minimum of adverse events [AEs], laboratory chemistry and hematology and electrocardiogram [ECG]), PK, and PD data (through Day 3)) were reviewed. The treatments for Part 2 are 60 mg GSK3389404 weekly, 120 mg bi-weekly GSK3389404, 120 mg GSK3389404 weekly or placebo.

A sentinel group will be dosed first and followed per the Time and Events Tables (Section 7.1). Safety data from all subjects in the sentinel group (1 subject from each active treatment group and the corresponding matching placebo) will be reviewed (must be at least 2 weeks of exposure, but may include more data). The safety review will be conducted by the GSK internal clinical team or Safety Review Team (SRT) in a blinded manner. Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure in all subjects in the sentinel group are reviewed.

Study treatment and post-treatment follow-up Time and Events Tables for weekly and bi-weekly (every 2 weeks) dosing regimens are provided in Section 7.1.

Figure 2 Part 2: Multiple Dose, Dose-Ranging, Study Design Schematic



1. HBeAg positive and negative subjects will be enrolled
2. Two separate randomization schedules will be used. One for the sentinel group and one to complete enrollment of Part 2 subjects. Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure in the sentinel group are reviewed.
3. The sentinel group will consist of at least 1 active and 1 placebo subject per each dosing level and regimen. Subjects enrolled in the sentinel group are dosed and followed per the Time and Events Tables. Safety data from all subjects in the sentinel group will be reviewed (must be at least 2 weeks of expsosure, but may include more data).
4. Matching placebo for each treatment arm (dose/regimen)
5. An optional Japanese Part 2 sub-study is planned. The exact details may be found in a country-specific protocol amendment/supplement and will not be detailed here. The Japan sub-study may include more intensive PK monitoring and/or potential overnight/hospital stay.

Since this is the first administration of GSK3389404 in subjects with CHB, the study design may change based on emerging data from each cohort and/or part. Certain aspects of the study design may be adjusted during the course of the study, including the proposed doses, dosing regimen, and/or dosing duration of GSK3389404, based on review of the safety, tolerability, PK, and/or PD results. Section 6.3 provides additional information regarding planned dose adjustments. The PK sampling scheme and/or assessments schedule may also be adjusted during the course of the study (in case of unexpected PK behavior).

The protocol may be amended to include additional part(s) to further explore the safety, tolerability, and PD of GSK3389404 in order to select an optimal dose level, regimen, and duration for subsequent evaluation in future studies.

4.2. Treatment Arms and Duration

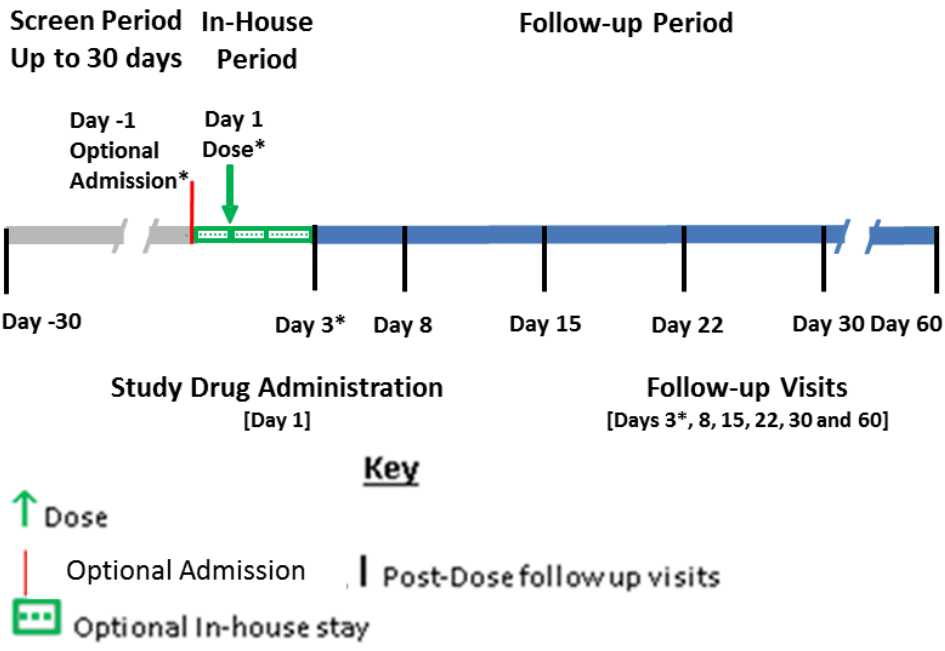
In Part 1, five dosing cohorts are planned (Figure 1), and the total study duration, including screening, treatment, and post-treatment follow-up, is not expected to exceed 13 weeks for each subject (Figure 3).

Subjects will receive a SC dose of GSK3389404 or placebo on Day 1 with post-treatment follow-up on Day 3.

- Based on subject and study site preference, subjects have the option to be domiciled at the study site or present to the study site as outpatients.
  - Admission to the study site is optional from Day -1 to Day 2.
  - Subjects admitted to the study site may be discharged Day 1, Day 2, or Day 3, based on subject and study site preference.
  - Subjects may present as outpatients on Day 1 and/or Day 3, based on subject and study site preference.

Subjects are required to return to the study site for post-treatment Follow-up visits on Days 3, 8, 15, 22, 30, and 60.

Figure 3 Part 1: Single Ascending Dose, Participation Flow

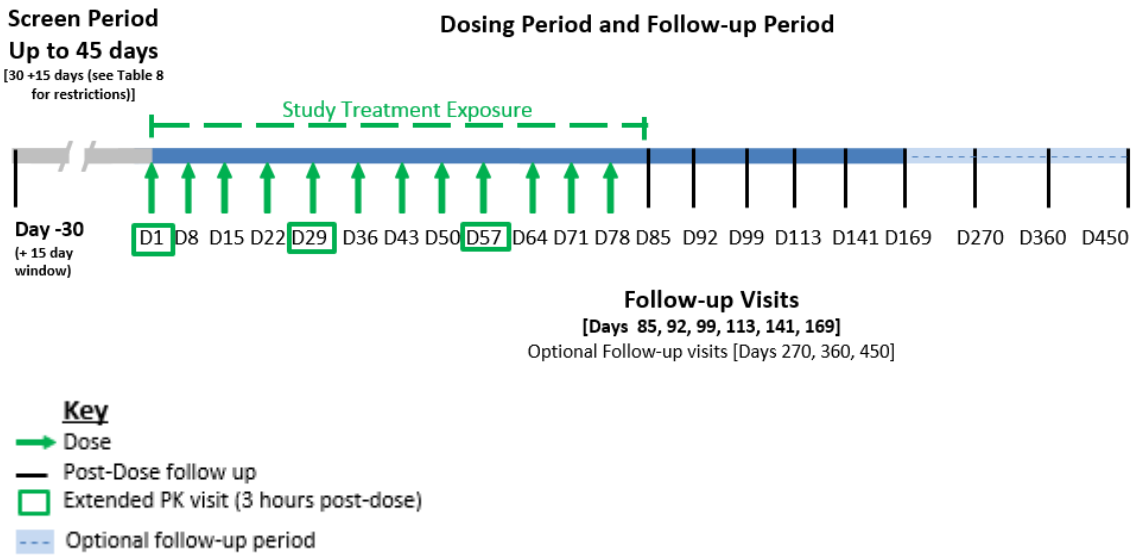


Note: Five cohorts are planned to receive a SC dose of GSK3389404 (30 mg to ≤240 mg) or placebo
*In-house stays are optional from Day -1 to Day 3 based on study site/subject preference. No study procedures are scheduled for Day 2 but subjects may remain in-house until all Day 3 assessments are completed.

In Part 2, the total study duration, including screening (and the 15 day window exceeding the normal 30 day screening window), treatment and post-treatment follow-up, is not expected to exceed 71 weeks for each subject (Figure 4 and Figure 5).

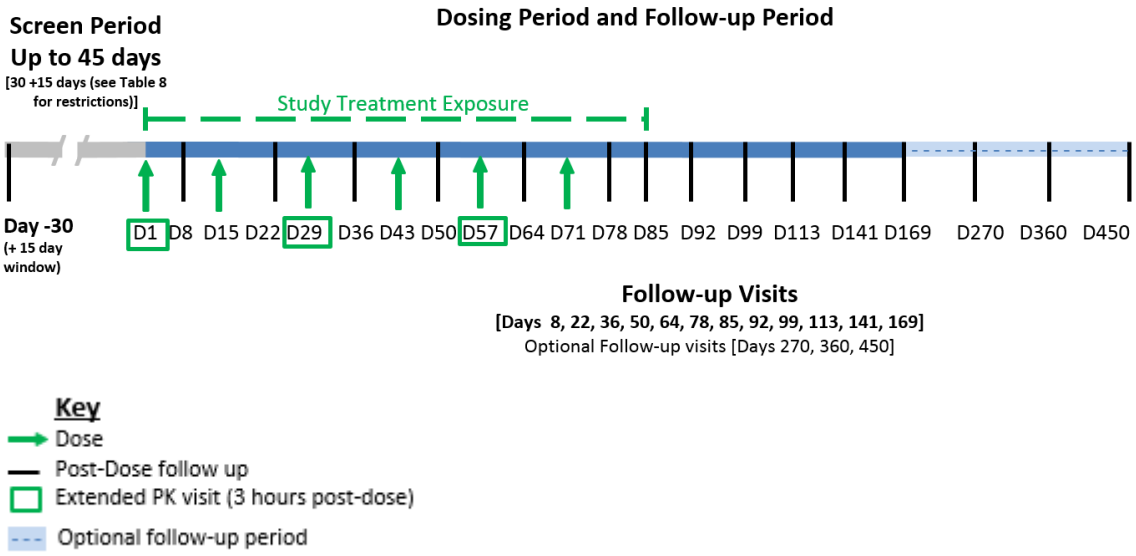
For once weekly dosing (Figure 4), study treatment will be administered weekly and subjects followed weekly in outpatient visits until the final dose (Day 78) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 85, 92, 99, 113, 141, and 169. An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.

Figure 4 Part 2: Multiple Dose, Dose-Ranging Participation Flow (Once a Week Dosing)



For bi-weekly (every 2 weeks) dosing (Figure 5), study treatment will be administered every 2 weeks and subjects followed weekly in outpatient visits until the final dose (Day 71) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 78, 85, 92, 99, 113, 141, and 169. An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.

Figure 5 Part 2 Multiple Dose, Dose-Ranging Participation Flow (Bi-weekly Dosing)



4.3. Type and Number of Subjects

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAg-negative subjects. For Part 2, both HBeAg-positive and/or HBeAg-negative subjects will be enrolled.

Approximately 73 subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, twelve subjects were enrolled. Originally, approximately 20 to 40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol.
- In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. There are approximately 11 subjects in each of the active treatment groups and approximately 6 subjects in the placebo group.
- If Japan participates in the optional Japanese Part 2 sub-study, approximately 22 subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement.

In Part 1, additional subjects/cohorts may be recruited to replace those who discontinue the study early (Section 5.4), to expand the size of selected existing cohorts, and/or to add intermediate cohorts (Section 6.3).

4.4. Design Justification

This first-in-patient study will evaluate safety, tolerability, PK, and PD of GSK3389404 across a wide range of doses projected to encompass the expected therapeutic dose range and for a dosing duration of up to 3 months in the target patient population (subjects with CHB).

The study is designed as a 2-part, randomized, placebo-controlled, double-blind (sponsor unblind in Part 1) dose ranging study to distinguish the effects of active dose levels and regimens in an efficient and unbiased manner. The sequential nature of Part 1 ensures that a range of single doses are investigated before exposing subjects to the highest planned dose (Cohort D). Safety, PK, and PD data from Part 1 will be reviewed prior to initiating Part 2 to identify the dose levels and regimens in Part 2 and to identify the HBV population (HBeAg-positive subjects only or HBeAg-positive- and negative subjects).

In Part 1, the planned starting dose is 30 mg. This starting dose is based on the review of data from the SAD portion of the recently completed clinical trial (Study 202007; at the time of this protocol writing, the final study report is in progress). To ensure continued safety in subjects with CHB, Dose Escalation Committee meetings will be incorporated between Part 1 cohorts (Section 10.8.1) with planned dose adjustments incorporated as needed (Section 6.3). Part 2 will be initiated after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the GSK study team and principal investigator (or appropriate designee) at the Dose Escalation Committee meetings for Part 1. A review of safety data (of at least 2 weeks exposure) from the sentinel group of Part 2 has been incorporated to ensure continued safety in subjects with CHB (Section 10.8.2). Safety data from all subjects will be reviewed by the GSK internal clinical team or SRT in a blinded manner on a regular basis thereafter. Randomization for the remainder of subjects in Part 2 will continue after this safety data review.

4.5. Dose Justification

The GSK3389404 dosing regimens selected for this study were based on observed human PK parameters, in vivo antiviral exposure-response relationship, and predicted safety margins relative to the 13- and 39-week no observed adverse effect level (NOAEL), AUC and C_{max} in monkeys [ISIS Study Number 712408-AS02, 2016; ISIS Study Number 712408-AS05, 2017]. The rationale for the selection of doses is presented below in Section 4.5.1 through Section 4.5.4. The actual dose levels, dosing regimens, or dosing duration in subjects with CHB may be adjusted during the course of the study based on human safety data, observed human PK, toxicological coverage, and clinical antiviral activity (PD data) at previous dose levels.

4.5.1. Observed Human Pharmacokinetics

GSK3389404 has been administered to healthy adult subjects in Study 202007 and in CHB adult subjects in Part 1 of this study (Study 205670).

Study 202007 was a Phase I, first time in human, randomized, double-blind, placebo controlled, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404. GSK3389404 was administered to healthy adult subjects as single SC doses at doses of 10 to 120 mg, or as repeated SC doses (once weekly for 4 weeks) at doses of 30 to 120 mg. At the time of this protocol amendment writing, the final study report for 202007 has been completed. The human PK parameters are presented in Table 1. Based on PK data, GSK3389404 showed dose proportional- PK with a mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose. The observed human PK data were evaluated using noncompartmental analysis (NCA) in Phoenix WinNonlin- version 6.3. All ISIS50538 (GSK3228836) plasma concentrations were below the LLOQ of 10 ng/mL.

In this study (Study 205670), GSK3389404 has been administered to CHB adult subjects as single SC doses at doses of 30 mg and 120 mg. At the time of this protocol amendment writing, CHB subjects have been administered GSK3389404 (at 30 mg and at 120 mg single dose). Based on the preliminary PK analysis, the mean half-life was approximately 4 to 5 hours at the dose of 30 mg and 120 mg in CHB subjects, consistent with that in healthy subjects. The observed human PK data were evaluated using noncompartmental analysis (NCA) in Phoenix WinNonlin- version 6.3.

Table 1 Summary of Selected Plasma GSK3389404 Pharmacokinetic Parameters in Healthy Adult Subjects

Dose (mg)	**10**	**30**			**60**			**120**		
Cohort[1]	A	B	E	E	C	F	F	D	G	G
Day	1	1	1	22	1	1	22	1	1	22
N	6	5[2]	6	6	6	6	6	6	6	6
Half life[3] (hr)	3.8 (66)	3.7 (81)	3.0 (34)	4.1 (61)	5.1 (71)	5.0 (206)	3.1 (51)	4.1 (29)	3.7 (43)	3.4 (38)
T_{max}[4] (hr)	1 (1-4)	2 (1-2)	2 (1-4)	2 (1-4)	3 (1-4)	2 (2-2)	2 (1.5-4)	4 (3-4)	2 (1.5-4)	2 (2-4)
C_{max}[3] (ng/mL)	90 (24)	295 (69)	228 (32)	194 (20)	512 (57)	692 (35)	577 (43)	803 (49)	1167 (50)	1107 (55)
$AUC_{(0-\infty)}$[3] (ng*hr/mL)	614 (27)	1969 (35)	1394 (24)	1526 (34)	4578 (30)	5875 (52)	3966 (23)	7718 (35)	8039 (36)	8640 (32)
Fold coverage C_{max}[5]	586	179	231	273	103	76	91	66	45	48
Fold coverage AUC[5]	802	250	353	323	108	84	124	64	61	57
Fold coverage C_{max}[6]	32	10	13	15	6	4	5	4	2	3
Fold coverage AUC[6]	22	7	10	9	3	2	3	2	2	2

1. Cohort A – D were single dose cohorts. Cohort E – G were multiple dose cohorts (weekly dose for 4 weeks).
2. In Cohort B (30-mg single) dose, the pharmacokinetic profile in one subject was atypical and not evaluable.
3. Data are presented as geometric mean (geometric coefficient of variation %).
4. Data are presented as Median (range).
5. Fold coverage based on exposure (AUC and Cmax) at NOAEL (no observed adverse effect level) of 13-week monkey study: Gender averaged C_{max} = 52.7 μg/mL and gender averaged $AUC_{(0-\infty)}$ = 492.7 μg•h/mL at NOAEL of 30 mg/kg/week.
6. Fold coverage based on exposure (AUC and Cmax) at NOAEL (no observed adverse effect level) of 39-week monkey study: Gender averaged C_{max} = 2.9 μg/mL and gender averaged $AUC_{(0-\infty)}$ = 13.5 μg•h/mL at NOAEL of 2 mg/kg/week.

4.5.2. Safety Margin Calculations

From the 13-week toxicology studies in mice and monkeys, the NOAELs were identified at 2 and 30 mg/kg/week, respectively [ISIS Study Number 712408-AS01, 2016; ISIS Study Number 712408-AS02, 2016]. The NOAELs of 26-week mouse and 39-week monkey studies were 6 and 2 mg/kg/week, respectively [ISIS Study Number 712408-AS04, 2017; ISIS Study Number 712408-AS05, 2017]. In general, rodents are more sensitive to the class-related pro-inflammatory effects of ASOs as compared to primates (including humans) and therefore, not considered an appropriate species for the

calculation of systemic safety margins [Henry, 2008]. Thus, only the monkey data were used to calculate the safety margin.

Based on observed PK data in healthy adult subjects (Study 202007), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is at least 45-fold lower than the C_{max} and AUC values at NOAEL of 13-week monkey study, and at least 2-fold lower than the C_{max} and AUC values at NOAEL of 39-week monkey study, respectively (Table 1). Based on the preliminary PK analysis in Part 1 of this study (Study 205670), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is lower than the C_{max} and AUC values at NOAEL of 13-week and 39-week monkey study.

Human liver concentrations were estimated based on liver tissue concentrations from the 13-week toxicology study in monkeys. This estimate suggests that a 30 mg dose in a human would yield liver concentrations 55-fold lower than the previously completed Phase I study with the parent compound, ISIS 505358 (Table 2). These data support the proposed 30 mg dose as a safe initial dose for this study.

Table 2 shows the observed and predicted human GSK3389404 PK, the predicted liver concentrations, and the fold safety margins of the predicted exposures after single, SC administration of GSK3389404 relative to the 13- and 39-week monkey NOAELs. In addition, liver concentration fold coverage based on the estimated human liver concentration of ISIS 505358 (parent) from a previously completed Phase I clinical trial is presented.

In addition, Bayesian predictive probabilities of $AUC_{(0-\infty)}$ and C_{max} less than the respective 13-week monkey study mean NOAEL were calculated for the 240 mg dose level using a power model and using observed data at 10, 30, 60 and 120 mg dose levels from Study 202007. The predictive probability of $AUC_{(0-\infty)}$ and C_{max} crossing the respective threshold values of 13-week monkey study mean NOAEL are very low (<0.01%) and are within the acceptable range (i.e. <50%) for the 240 mg treatment group.

Table 2 GSK3389404 Plasma C_{max} and AUC and Monkey NOAEL Exposure Fold Coverage Following Single SC Administration of GSK3389404 in Humans

Human Dose (mg)	Observed GSK3389404 Plasma C_{max} (ng/mL)[1]	Observed GSK3389404 Plasma AUC (h•ng/mL)[1]	Predicted Parent Liver Concentration (μg/g)[2]	Fold Coverage Plasma Based on 13-week monkey study NOAEL[3]		Fold Coverage Plasma Based on 39-week monkey study NOAEL[4]		Fold Coverage Of Estimated Human Liver Concentration from Phase I Parent Study[5]
				C_{max}	AUC	C_{max}	AUC	
10	90	614	2.8	586	802	32	22	161
30	295	1968	8.2	179	250	10	7	55
60	512	4578	16.2	103	108	6	3	28
120	803	7718	31.4	66	64	4	2	14
240	1728[6]	15992[6]	59.0	30	31	2	0.8	8

NOAEL = no observed adverse effect level

1. Geometric mean of GSK3389404 plasma human PK observed at 10 to 120 mg in Study 202007 and predicted for 240 mg.
2. Liver concentration in monkeys at 1 week after a single dose was approximately 20% of that at 13 weeks (steady state) after repeated once weekly doses. Human steady state liver concentration of parent compound (ISIS 505358) was estimated based on 13-week monkey liver tissue concentration and assumed to be 20% that of steady state. Liver concentration was fit to an E_{max} model and then extrapolated.
3. Fold coverage based on 13-week monkey study NOAEL; GSK3389404 gender averaged plasma C_{max} = 52.7 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 492.7 μg•h/mL at 30 mg/kg/week.
4. Fold coverage based on 39-week monkey study NOAEL; GSK3389404 gender averaged plasma C_{max} = 2.9 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 13.5 μg•h/mL at 2 mg/kg/week.
5. At 450 mg of ISIS 505358 (the highest dose tested in ISIS 505358 first time in human study), human liver concentration (4 weeks) = 450 μg/g, based on allometric scaling [Geary, 2009]. Fold coverage = 450 μg/g divided by the predicted liver concentration.
6. Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (10 to 120 mg) given dose proportionality.

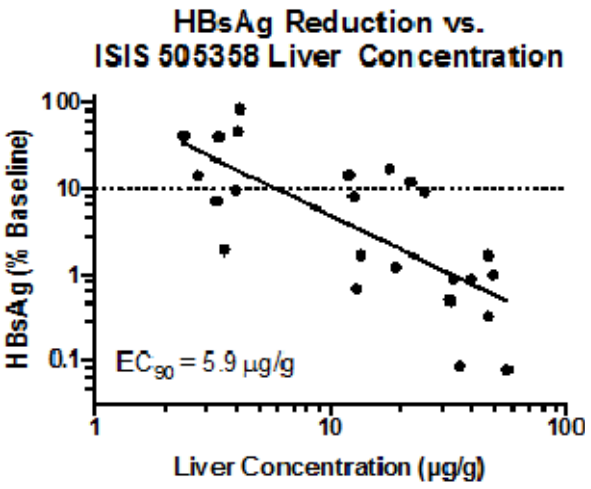
4.5.3. In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds

The maximum planned dose in the multiple dose cohorts (total monthly dose not exceeding 480 mg GSK3389404) was selected based on the in vivo exposure-response relationship of GSK3389404.

ISIS 505358 is the parent compound of the prodrug GSK3389404, and is currently being studied in HBV infected subjects. Therefore, no direct antiviral activity data with ISIS 505358 from humans are available for extrapolation. To establish an exposure-response relationship, an in vivo efficacy study of GSK3389404 dosed once weekly for 4 weeks and ASO's liver tissue concentrations were measured in HBV transgenic mice.

GSK3389404 reduced hepatic HBV RNA and DNA in the HBV transgenic mice. Administration of GSK3389404 dose-dependently reduced serum HBsAg levels within 7 days and reduced serum levels of antigen were maintained for the 4-week period of testing. Maximal reduction of serum HBsAg was approximately 99% (2 logs), and liver concentration that produces 90% of maximal effect (EC_{90}) was 5.9 µg/g and concentration that produces 99% of maximal effect (EC_{99}) was 33 µg/g (Figure 6).

Figure 6 Liver EC_{90} of ISIS 505358 from GSK3389404-Treated HBV Transgenic Mice



ASO = antisense oligonucleotides, EC_{90} = concentration that produces 90% of maximal effect
Notes: Mice were treated with vehicle, control ASO (ISIS 716837 at 10 mg/kg/week) or various doses (1, 3 or 10 mg/kg/week) of GSK3389404 for 4 weeks. Serum HBsAg levels at the end of treatment were plotted against the observed liver concentration of ISIS 505358. The EC_{90} was calculated from log/log transformed values using linear regression analysis (GraphPad Prism 6), which is shown as the solid line in graph (N=8 mice per group).

In the GSK3389404 HBV transgenic mice study, tissue analysis indicated the GalNAc moiety was completely removed in the liver for all oligonucleotide treatments. Only unconjugated parent ASO, ISIS 505358, was observed and quantified in the liver.

Thus, in order to knockdown the target gene 99%, these data suggest that Study 205670 should explore SC doses of GSK3389404 predicted to yield human liver tissue concentrations of ISIS 505358 that will achieve EC_{99} (33 μg/g). Based on observed liver tissue concentration in the monkey, it is estimated that a 30 mg weekly SC injection of GSK3389404 would reach a human liver tissue concentration of 41 μg/g (>EC_{99}) after 13 weeks, assuming the liver tissue concentration between monkey and human is similar on a mg/kg basis (Table 3). However, greater clinical efficacy may be achieved if HBsAg is reduced by >99%.

Table 3 GSK3389404 Plasma C_{max} and AUC and Monkey NOAEL Exposure Fold Coverage Following Repeat Weekly or Bi-weekly (every 2 weeks) SC Administration of GSK3389404 for 13 Weeks in Humans

Human Total Monthly Dose (mg)	Human Repeat Dose (mg)[1]	Observed GSK3389404 Plasma		Predicted Parent Liver Concentration at Week 13 (μg/g)[3]	Observed Fold Coverage		Fold Coverage of Predicted Human Liver Concentration at Week 13[6]	Observed Fold Coverage		Fold Coverage of Predicted Human Liver Concentration at Week 13[6]
		C_{max} (ng/mL)[2]	AUC (h•ng/mL)[2]		Plasma C_{max}[4]	Plasma AUC[4]		Plasma C_{max}[5]	Plasma AUC[5]	
120	30 QW	194	1526	41	272	323	34	15	9	4
240	60 QW	577	3966	81	91	124	17	5	3	2
480	120 QW	1107	8640	157	48	57	9	3	2	1
480	240 Q2W	2200	16769	157	24	29	9	1	0.8	1

NOAEL = no observed adverse effect level

1. QW: dose every week. Q2W: dose every 2 weeks.
2. Geometric mean of GSK3389404 plasma human PK observed following repeat weekly SC dose of 30 to 120 mg for 4 weeks in Study 202007. The values for 240 mg were predicted
3. Human liver concentration of parent compound (ISIS 505358) at Week 13 was estimated based on 13-week monkey liver tissue concentration (an average of 1404 μg/g at 30 mg/kg/week for 13 weeks). Liver concentration was fit to E_{max} model and then extrapolated.
4. Fold coverage based on 13-week monkey study NOAEL (30 mg/kg/week): gender averaged plasma GSK3389404 C_{max} = 52.7 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 492.7 μg•h/mL. Gender averaged liver tissue concentration of parent compound (ISIS 505358) = 1404 μg/g.
5. Fold coverage based on 39-week monkey study NOAEL (2 mg/kg/week): gender averaged plasma GSK3389404 C_{max} = 2.9 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 13.5 μg•h/mL. Gender averaged liver tissue concentration of parent compound (ISIS 505358) = 176 μg/g.
6. Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (30 to 120 mg) given dose proportionality

4.5.4. Dose Escalation Justification

The planned GSK3389404 doses for this study are 30, 60, 120 and 240 mg administered by SC injection for the single dose cohorts (Part 1). The proposed doses of GSK3389404 may be adjusted during the course of the study as the safety, PK, and PD results are reviewed. Doses in Part 2 will be selected such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma C_{max} and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time ($AUC_{(0-\infty)}$) observed at

- the NOAEL of 30 mg/kg/week in the 13-week monkey toxicity study (C_{max} = 52.7 µg/mL; $AUC_{(0-\infty)}$ = 492.7 µg•h/mL) and
- the NOAEL of 2 mg/kg/week in the 39-week monkey toxicity study (gender averaged C_{max} = 2.9 µg/mL; $AUC_{(0-\tau)}$ = 13.5 µg•h/mL).

Escalation to the next higher single dose or to Part 2 will only proceed after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and the investigator at the Dose Escalation Committee meeting (Section 10.8.1) and determined to be safe, tolerable, and supportive of escalation.

4.5.5. GSK3389404 and Nucleos(t)ides

GSK3389404 is unlikely to be a victim or perpetrator of drug-drug interactions when administered with nucleos(t)ides due to their divergent absorption, distribution, metabolism, and excretion pathways.

Victim drug-drug interactions:

GSK3389404 is taken up into the liver by target mediated endocytosis and into the kidney by micropinocytosis, both routes that are not inhibited by small molecule drugs such as tenofovir, entecavir, lamivudine, adefovir and telbivudine. Furthermore, GSK3389404 is metabolized by endogenous endonucleases, which are not inhibited by these 5 drugs.

Perpetrator drug-drug interactions:

Tenofovir, entecavir, lamivudine, adefovir and telbivudine are predominantly renally eliminated from systemic circulation [Lamivudine, 2002; Kearney, 2004; Adefovir , 2012; Telbivudine, 2013; Entecavir, 2015]. 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].

In a recent study, a model compound of 2'-O-(2-methoxyethyl) modified antisense oligonucleotide was shown to be neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2 [Yu, 2016]. Therefore, GSK3389404, or the primary tissue metabolite ISIS 505358 that was shown to be extensively distributed into the kidney in non-clinical

studies, is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK3389404 can be found in the IB [GlaxoSmithKline Document Number 2015N236049_04]. This section outlines the risk assessment and mitigation strategy for this protocol.

4.6.1. Risk Assessment

Based on findings in nonclinical studies of GSK3389404 and nonclinical studies of related compounds, the following areas of interest have been identified and appropriate risk mitigation strategies have been adopted as summarized in Table 4.

Additional withdrawal/stopping criteria for liver chemistry, QT interval corrected for heart rate (QTc), hematology, renal function, and PK are discussed in Section 5.4. Planned dose adjustments are outlined in Section 6.3.

Table 4 Summary of Key Issues, Their Impact, and Strategy to Mitigate Risk

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
Liver Effects: In the 13-week GSK3389404 mouse study, doses ≥6 mg/kg/week caused increases in liver enzymes (9.4 X AST, 7.5 X ALT, 1.6 X ALP and/or 1.7 X bilirubin) with correlating histopathology changes which include minimal to mild hepatocellular hypertrophy, vacuolated macrophages and scattered single cell hepatocyte necrosis with evidence of reversibility following the 13-week recovery period. The mean liver concentration (13.5 μg/g) at the NOAEL of 2 mg/kg/week in the mouse is approximately 0.4- to 2.3-fold higher than the predicted clinical efficacious liver concentration range (EC_{90}-EC_{99}: 5.9 to 33 μg/g). In the 26-week mouse study, liver findings (eosinophilic hepatocytes, individual hepatocyte necrosis, presence of macrophages with vacuolated/granular cytoplasm (sinusoidal macrophages) and/or accumulations of pigmented macrophages, and karyomegaly.) without clinical chemistry correlates were not considered adverse. Liver concentration of ISIS 505358 (97.8 μg/g) at the NOAEL of 6 mg/kg/week in male mice was 16.6- to 3.0-fold of predicted clinical efficacious liver concentrations (EC_{90}-EC_{99}: 5.9 to 33 μg/g). The 42 to 238-fold higher liver concentrations (gender averages 1403 μg/g) were achieved at the NOAEL of 30 mg/kg/week in the 13-week monkey study. In the 39-week monkey study, the liver concentration of ISIS 505358 (176 μg/g) at the NOAEL of 2 mg/kg/week was approximately 29.8- to 5.3-fold of predicted clinical efficacious liver concentration (EC_{90}-EC_{99}: 5.9 to 33 μg/g). In the ISIS 505358-CS1 Phase I study in healthy subjects, modest (1.03 to 1.41 X ULN) elevations in ALT that were	Exclusion Criteria: Subjects with a history or active diagnosis of liver disease other than CHB are excluded (Section 5.2, exclusion criterion 1). Subjects with liver cirrhosis or evidence of cirrhosis are excluded (Section 5.2, exclusion criterion 4). Subjects with laboratory test results suggestive or indicative of advanced liver disease are excluded (Section 5.2, exclusion criterion 8). Subjects with co-infection with HDV are excluded (Section 5.2, exclusion criterion 7).	**Subject Assessments:** Frequent assessment for clinical symptoms suggestive of liver dysfunction (e.g., abdominal pain, yellowing of eyes, changes in urine color, etc.). **Laboratory Evaluations:** Frequent laboratory assessment of liver function including AST, ALP, GGT, bilirubin (total and direct), albumin, INR, PT, aPTT. **Stopping Criteria:** Individual subject liver chemistry stopping/increased monitoring criteria have been specified and required assessments for subjects that meet the criterion are defined in the protocol (Section 5.4.1).

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
transient and not associated with concurrent symptoms or increases in bilirubin were observed. All subjects with elevated ALT returned to baseline during post-treatment follow-up. In the GSK3389404 Phase 1 study in healthy subjects (Study 202007), in Part 1 single dose, two subjects experienced mild or moderate adverse events associated with elevations in ALT. Both were transient, modest (DAIDs criteria Grade 1 (<2.5x ULN)) and not associated with concurrent symptoms or increases in bilirubin. In Part 2 multiple dose, no liver-chemistry related AEs were reported.		
Coagulation Effects: In the 13-week GSK3389404 monkey study, acute and transient test article-related changes in the coagulation included slightly prolonged (up to 5.1 seconds higher than the baseline value) aPTT values at 30 mg/kg/week. The prolongation was observed 4 hours after dosing on Days 1 and 91 and generally returned to baseline by 24 hours post-dose. These results are consistent with the aPTT results from the clinical and nonclinical studies of other phosphorothioate and MOE-modified phosphorothioate ASOs [Dorr, 2001; Levin, 2001; Henry, 2008; Kwoh, 2008]. In the ISIS 505358-CS1 Phase I study in healthy subjects, aPTT prolongations were observed at 3 to 5 hours post injection of ISIS 505358. The magnitudes of this prolongation were modest, not clinically significant and generally resolved within 12 to 24 hours after dosing. There was no test article-related coagulation prolongation in monkeys treated with GSK3389404 at doses up to 8 mg/kg/week for 39 weeks. In Study 202007, the GSK 3389404 Phase 1 study in	Exclusion Criteria: Subjects with a history of bleeding diathesis or coagulopathy will not be enrolled (Section 5.2, exclusion criterion 1e). Subjects with platelet count <140 X 109/L are excluded (Section 5.2, exclusion criterion 8d).	**Subject Assessments:** Subjects monitored for signs and symptoms of bleeding, hemorrhage, or bruising. **Laboratory Evaluations:** Frequent laboratory assessments of coagulation parameters (i.e., aPTT, PT, INR) and hematological function (i.e., hemoglobin, ANC, and platelets).

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
healthy subjects, there was no evidence of GSK3389404 related prolongation of aPTT.		
Complement Activation: In the monkey GSK3389404 13-week study, minimal decreases in (up to 21% from baseline) C3 and increased complement fragment Bb (up to 3.6-fold over baseline) were observed in the 8 and 30 mg/kg groups, suggesting mild activation of the alternative complement pathway. The significance of these findings remains unclear because there was also an 11% decrease in C3 observed in male controls. These changes in aPTT, C3, Bb, ALT, and IgM were not seen during the 13-week recovery period. In the 39-week monkey study, there was a mild and transient increase in complement fragment Bb (up to 2.1-fold over baseline compared to up to 1.4-fold over baseline in control) and decrease in C3 concentrations in individual animals at ≥ 0.5 mg/kg/week. These changes were not considered adverse since they were mild and transient. In the ISIS 505358-CS1 Phase I study in healthy subjects, no effect of ISIS 505358 administration on complement activation was observed. In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, no effect of GSK3389404 administration on complement (C3, C4, C5a or Bb) was observed.	**Exclusion Criteria:** Subjects with history of or suspected vasculitis are excluded (Section 5.2, exclusion criterion 1h). Subjects with a history of extrahepatic disorders possibly related to HBV immune complexes (e.g., glomerulonephritis and polyarteritis nodosa) will be excluded (Section 5.2, exclusion criterion 1e).	**Subject Assessment:** Subjects monitored for signs and symptoms of generalized systemic inflammation, vasculitis and infection and evaluated immediately if an inflammatory event or infection is suspected. **Laboratory Evaluations:** Frequent assessment of inflammation-related markers to provide surveillance for detecting inflammation and vascular effects. These include measurement of hs-CRP (as specified in the Time and Events Tables [Section 7.1]), complement factors C3 and C4 (as specified in the Time and Events Tables [Section 7.1]), and the complement split products Bb and C5a (reflexive testing). Further, the acute phase reactants albumin and platelets, (changes in which may signal an acute phase response) will be assessed. Should any of this testing yield a result suggestive of an inflammatory event, measurements of cytokines, chemokines and/or autoimmune antibodies may be performed.
Pro-inflammatory Effects/Constitutional or Flu-Like Symptoms: At doses of ≥2 mg/kg/week GSK3889404 in the 13-week mouse study, vacuolated macrophages and mixed cell leucocytes were increased in incidence and/or magnitude at the site of injection compared to controls. In the 26-week mouse study, minimal to mild vacuolated/granular macrophages and increased incidence of mixed leukocytes were noted at the injection sites and/or	**Exclusion Criteria:** Subjects with history of or suspected vasculitis are excluded (Section 5.2, exclusion criterion 1g). Subjects with a history of extrahepatic disorders possible related to HBV immune complexes (e.g., glomerulonephritis and polyarteritis nodosa) will be excluded (Section 5.2, exclusion criterion 1e).	**Subject Assessment:** Subjects clinically monitored for influenza/constitutional symptoms (e.g., fever, chills, arthralgias, and respiratory symptoms). Subjects frequently assessed for the occurrence of injection site reactions (ISRs) and graded for severity based upon DAIDS criteria including assessments of pain,

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
non-injected skin sections in both sexes at doses of ≥0.5 mg/kg/week. However, these findings are considered to reflect the sensitivity of rodents to proinflammatory effects of ASOs [Henry, 2008] and evidence of reversibility was seen in the recovery interval. There were no significant injection site findings in the 13- and 39-week monkey studies at doses up to 30 and 8 mg/kg/week, respectively. In humans, influenza-like/constitutional symptoms such as fever, chills, and arthralgias have been observed following SC administration of other phosphorothioate and MOE-modified phosphorothioate ASOs. If these constitutional symptoms occur, they generally arise shortly after dosing and resolve within 24 to 48 hours. In the ISIS 505358-CS1 Phase I study in healthy subjects, administration-proximal constitutional symptoms were not observed. In Study 202007, the GSK3389404 Phase 1 study in healthy subjects, influenza-like/constitutional symptoms such as fever, chills and arthralgias were not observed. Injection site reactions were the most commonly reported treatment-related adverse event. These AEs were mild in intensity, transient in nature and not related to dose or duration of treatment.		erythema, swelling and pruritus. Injection site reaction events meeting SAE criteria or Grade 3 DAIDS severity (by any measure) will be documented by photography. Events meeting SAE criteria or Grade 3 DAIDS severity (by any measure) or persisting beyond 2 weeks post-dose will be considered for potential dermatology consultation. **Laboratory Evaluations:** Hematologic profiles including complete blood count with total WBC counts and differential counts will be frequently monitored. Plasma levels of hs-CRP, an inflammation related marker, are measured frequently throughout the study and samples stored for cytokine analysis, if required.
Kidney Effects: No adverse kidney findings were observed in the mouse (up to 24 mg/kg/week) and monkey (up to 30 mg/kg/week) 13-week GSK3389404 studies, and in mice (up to 6 mg/kg/week) and monkeys (up to 8 mg/kg/week) following 26 and 39 weeks of repeat dosing, respectively. The presence of basophilic granules in the tubular epithelium in both species and occasionally	**Exclusion Criteria:** Subjects with a history or active diagnosis of renal disease, either primary or secondary (e.g. renal disease due to diabetes, hypertension, vascular disease, etc.) are excluded (Section 5.2, exclusion criterion 1d); Subjects with serum creatinine >ULN, glomerular filtration	**Subject Assessments:** Subjects assessed for clinical symptoms suggestive of renal dysfunction (e.g., changes in urine output, color and blood). Subjects will have frequent laboratory assessments of renal function including creatinine, phosphate and albumin in serum and protein, creatinine, blood and glucose in urine. GFR and urine ACR are calculated frequently.

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
vacuolated/granular macrophages surrounding the pelvic region of kidneys in mice are considered indicative of cellular uptake of oligonucleotides. These findings were generally reversible by the end of recovery period, and therefore, were not considered adverse [Henry, 2000]. In humans administered 2'-MOE ASOs, no trends in laboratory parameters of kidney function test have been identified that suggested an effect on renal function. In the ISIS 505358-CS1 Phase I study in healthy subjects, no changes in serum creatinine levels or other measures of renal function were observed. In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, no changes in the mean values from baseline for serum creatinine were observed.	rate (GFR) <90 mL/min (but ≥ 60 ml/min may be considered after consultation with the GSK medical monitor), or urine albumin to creatinine ratio (ACR) ≥0.03 mg/mg (or ≥30 mg/g).are excluded (Section 5.2, exclusion criteria 8e, 8f, and 8g). Subjects with a positive test for blood in urine are excluded if repeat testing reveals >5 RBC per HPF Section 5.2, exclusion criterion 9).	**Stopping Criteria:** If the following are observed, results should be confirmed and if confirmed, further evaluation pursued in consult with the GSK medical monitor: • Persistent urine ACR ≥0.03 mg/mg (or ≥30 mg/g). and without alternative cause(s) identified. • Blood in urinalysis ≥5 RBC per HPF confirmed by microscopy without alternative cause(s) identified. • Persistent elevation of serum creatinine (>26.52 μmol/L change from baseline) without an alternative cause identified. Following confirmation of the criteria above, further evaluation may include but not be limited to 24-hour urine for analysis, consultation with a nephrology specialist, renal ultrasound, urine microscopy, serum creatinine, SPEP/UPEP, and/or complement panel (C3, C4, C5a and Bb).
Decreased hematological parameters: No significant test article related changes in platelets were observed in the 13-week GSK3389404 mouse or monkey toxicity studies. In the 39-week monkey study, a marked and transient decrease in platelet count was noted in one male monkey administered GSK3389404 at 8 mg/kg/week on Day 184. The platelet count in this monkey returned to near baseline values by Day 191, despite continued treatment with test article. No significant test article-related changes in platelets were observed in the 26-week mouse study. In the 39-week monkey study, one high dose male had severe non-regenerative and potentially haemolytic anemia characterized by decreased red blood cell parameters and accompanied by decreased neutrophil counts, inflammation, renal injury/proteinuria, complement	**Exclusion Criteria:** Subjects with a history of bleeding diathesis or coagulopathy will not be enrolled (Section 5.2, exclusion criterion 1f). Subjects with platelet counts <140 x 109/L are excluded (Section 5.2, exclusion criterion 8d).	**Subject Assessments:** Subjects monitored for signs and symptoms suggestive of effects on white cell, red cell, or platelet production; these include signs or symptoms suggesting infection, anemia, bleeding, hemorrhage, or bruising. Adverse events indicative of bleeding will be evaluated. **Laboratory Evaluations:** Frequent laboratory assessments for WBC, hemoglobin, reticulocyte count and platelets. Further, RBC counts and red cell indices (e.g., red cell distribution width, mean corpuscular hemoglobin), will be followed. Laboratory values suggestive of hemolysis (e.g., bilirubin and lactate dehydrogenase) will be followed. **Stopping Criteria:** Individual subject hematological stopping criteria (Section 5.4.3) will be applied as follows: • Hemoglobin ≤9.9 g/dL

Potential Risk[1]/Summary of Data	Impact—Eligibility Criteria	Strategy— Monitoring/Stopping Criteria
activation, metabolic acidosis, and decreased nutrient uptake. This animal was sacrificed on Day 218 (Week 32). Since non-regenerative anemia and other associated findings were only noted in this one animal, and have not been noted in other studies with antisense oligonucleotide therapies, even when accompanied by complement activation and/or proteinuria, the relationship of anemia to treatment in this case is unclear. Platelet reductions have been observed in the clinical and preclinical studies of a few members of 2'-MOE ASO drug class. In the most cases, reductions in platelets have been mild and reversible. However, there have been reports of severe thrombocytopenia requiring medical intervention. In the ISIS 505358-CS1 phase 1 study in healthy subjects, laboratory data did not suggest any effect on hematological cell counts or hemoglobin. In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, the laboratory data did not suggest any GSK3389404 related effect on hematological cell counts or hemoglobin.		• ANC $\leq$750/mm^3 • Platelets $\leq$75 X 10^9/L

AE = adverse event, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, aPTT = activated partial thromboplastin time, ASO = antisense oligonucleotides, AST = aspartate aminotransferase, C3, C4 =complement factors 3 and 4, DAIDS = Division of Acquired Immune Deficiency Syndrome, ECG = electrocardiogram, GFR = glomerular filtration rate, GGT = gamma glutamyl transpeptidase, hs-CRP = high-sensitivity C-reactive protein, IB = Investigator's Brochure, INR = international normalized ratio, ISR = injection site reaction, MOE = methoxyethyl, NOAEL = no observed adverse effect level, PT = prothrombin time, RBC = red blood cell, SAD = single ascending dose, SAE = serious adverse event, SC = subcutaneous, SPEP = serum protein electrophoresis, UA = urinalysis, ULN = upper limit of normal, UPEP = urine protein electrophoresis, WBC = white blood cell

1. Additional details regarding potential risks identified in nonclinical toxicity studies as well as overall guidance for the clinical investigator are provided in the ISIS 505358 Hepatitis B Antisense Oligonucleotide. Investigators Brochure [available on request] [ISIS 505358, 2016].

4.6.2. Benefit Risk Summary

This first-in-patient study will evaluate safety, tolerability, PK, and PD of GSK3389404 across a range of doses projected to encompass the expected therapeutic dose range and for a dosing duration of up to 3 months in the target patient population (i.e., subjects with CHB). The intent of this study is to enable selection of an optimal dose level and regimen of GSK3389404 for subsequent evaluation in future studies.

It is not known if there will be any direct therapeutic benefit to the CHB population that will be included in this study. However, their participation could potentially contribute to the development of an improved treatment for subjects with CHB.

The study design mitigates risk to subjects through the following:

1. Inclusion/Exclusion criteria ensuring the enrollment of subjects with CHB who are without underlying organ dysfunction or significant co-morbidities that would put them at greater risk for potential drug-specific toxicities.
2. During Part 1 (SAD), dosing is sequential and subjects closely monitored for at least 8 hours post-dose. Subjects have extended follow-up out to 60 days post-dose to assess safety. A low starting dose, based on the fold coverage to mean NOAEL in the 13-week monkey toxicity study, was selected for the initial dose in Part 1.
3. In Part 1, dose escalation will be stopped or a smaller dose increment selected when the predicted mean $AUC_{(0-\infty)}$ and C_{max} of the next dose level are expected to exceed the NOAEL exposures observed in the 13-week monkey toxicity study (Section 6.3).
4. Between each dosing cohort in Part 1, escalation to the next dose-level will proceed only after the safety (AE listings, flagged vital signs, ECGs, laboratory findings [including liver function tests]) of the previous dose level, and PK results derived from 24-hour plasma profiles, together with available PD data) are thoroughly reviewed by the study team and the investigator at scheduled Dose Escalation Committee meetings (Section 10.8.1).
5. Safety, PK, and PD data from Part 1 will be reviewed prior to initiating Part 2 (multiple-dose) to identify the dose levels and regimens in Part 2.
6. In Part 2, safety data from a sentinel group (1 subject from each treatment group and the corresponding matching placebo) will be reviewed by the GSK internal clinical team or SRT in a blinded manner (Section 10.8.2). Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure (but may include more data) in the sentinel group are reviewed. Safety data from all subjects will be reviewed by the GSK internal clinical team or SRT in a blinded manner on a regular basis thereafter.
7. In Part 2, subjects are seen at the clinic on a weekly basis and safety assessments (AE/serious adverse event [SAE] review, physical exam, vital signs, ECG assessments) and comprehensive laboratory testing is performed

on a weekly or bi-weekly (every 2 weeks) basis. At the end of the 3-month treatment period, subjects will continue to have regular assessments during the post treatment follow-up period.

8. In both Parts 1 and 2, the protocol applies comprehensive and frequent safety monitoring with individual subject stopping criteria (Section 5.4) specified for key class and potential drug specific toxicities, including liver chemistry stopping criteria, QTc stopping criteria, hematological stopping criteria, renal function stopping criteria, and PK stopping criteria (Part 1 only). In addition, the protocol defines criteria, based on the occurrence of AEs of Grade 3 or Grade 4 severity, unacceptable pharmacological effects, or SAEs, when subject dosing or dose escalation is to be halted until a full safety review of the study has been undertaken (Section 6.3).

4.6.3. Overall Benefit:Risk Conclusion

Based upon the safety strategies and risk mitigations inherent to this protocol and the potential contributions to the development of an improved treatment for patients with CHB, it is concluded that there is a positive risk benefit to subjects for participation in this study.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

This first-in-patient study will enroll adult male and female subjects in either the immune tolerant or the immune active phase of HBV infection who may or may not be on a stable nucleos(t)ide regimen. The immune tolerant phase is characterized by the absence of biochemical symptoms of the disease (i.e., elevated transaminase levels). The immune active phase, also referred to as HBeAg-positive or HBeAg-negative chronic hepatitis, is characterized by elevated alanine aminotransferase (ALT) levels, evidence of active hepatic inflammation, and HBV DNA levels greater than or equal to 2000 IU/mL. Subjects who are on a stable nucleos(t)ide regimen are characterized by ALT levels less than or equal to the upper limit of normal (ULN) and have suppressed HBV DNA, defined as HBV DNA less than or equal to the lower limit of quantification (LLOQ). The entry criteria for this study are designed to enroll subjects with CHB who do not have advanced liver fibrosis or cirrhosis, other advanced concomitant liver diseases, co-infection, or other significant co-morbidities that would confound the safety monitoring and/or potentially put them at greater risk for treatment-related AEs.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK3389404 or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number 2015N236049_04].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in this section is essential.

A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria and are reported as outside of the

laboratory's reference range may be repeated and the subject included only if the investigator considers the finding unlikely to introduce additional risk to the subject and will not interfere with the study procedures.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Subject is able to understand and is capable of giving written informed consent, is willing to comply with protocol requirements, instructions and protocol-stated restrictions, and is likely to complete the study as planned.

2. Between 18 and 70 years of age, inclusive, at the time of signing the informed consent form.

3. A body mass index (BMI) between 18 to 30 kg/m^2, inclusive.

4. Male or female if they satisfy the following:

    a. All females must meet the following criteria:

        i. Non-pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test); AND

        ii. Non-lactating at screening and prior to dosing; AND

    b. Females of reproductive potential (FRP), must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until Follow-up visit Day 169 in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

    c. For females of non-reproductive potential, at least one of the following conditions must apply:

        i. Premenopausal females without reproductive potential defined by one of the following:

            1. Documented salpingectomy;

            2. Hysterectomy;

            3. Documented bilateral oophorectomy.

        ii. Postmenopausal defined as 12 months of spontaneous amenorrhea.

iii. A blood sample for simultaneous follicle-stimulating hormone (FSH) and estradiol levels may be collected at the discretion of the investigator or site to confirm non-reproductive potential. Please refer to laboratory reference ranges for confirmatory levels for menopause.

d. Male subjects with a female partner of child-bearing potential must agree to meet one of the contraception requirements from the time of first dose of study treatment until Follow-up visit Day 169.

i. Vasectomy

ii. Male condom plus partner's use of one of the contraceptive options below that meets the standard operating procedure (SOP) effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

e. Male subjects must refrain from donating sperm from the time of first dose of study treatment until Follow-up visit Day 169.

5. Documented chronic HBV infection ≥6 months prior to screening.
6. Subject with HBV treatment history as follows:
   a. Part 1:
      i. Treatment naïve, -or-
      ii. Have had prior treatment with interferon (pegylated or non-pegylated) that must have ended at least 6 months prior to the Baseline visit (Day 1 pre-dose) and/or nucleos(t)ide analogue therapy that must have ended at least 6 months prior to the Baseline visit -or-

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

b. Part 2: Subjects with CHB receiving stable nucleos(t)ide analogue therapy, defined as no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study. Subjects with prior treatment with interferon (pegylated or non-pegylated) must have ended treatment at least 6 months prior to the Baseline visit (Day 1 pre-dose).

7. Plasma or serum HBV DNA concentration:

   a. Treatment naïve subjects or subjects not currently receiving treatment, there is no minimum HBV DNA requirement.

   b. Subjects who are receiving stable nucleos(t)ide analogue therapy must be adequately suppressed, defined as plasma or serum HBV DNA <LLOQ.

8. Plasma or serum HBsAg concentration >50 IU/mL.

9. Alanine aminotransferase (ALT) concentration:

   a. ALT < 5 X ULN for treatment naïve subjects and for subjects who are not currently receiving treatment

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

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Medical history

   a. History of or active diagnosis of moderate to severe liver disease other than CHB, such as autoimmune hepatitis, non-alcoholic steatohepatitis, hemochromatosis, or liver failure.

   b. History or other clinical evidence of significant or unstable cardiac disease (e.g., prolonged QT syndrome [torsade de pointes], angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease and/or clinically significant ECG abnormalities).

   c. Uncontrolled or history of difficult to control hypertension.

   d. History of, or active diagnosis of, primary or secondary renal disease (e.g., renal disease secondary to diabetes, hypertension, vascular disease, etc.).

   e. History of extrahepatic disorders possibly related to HBV immune complexes (e.g., glomerulonephritis and polyarteritis nodosa).

   f. History of bleeding diathesis or coagulopathy.

g. History of or suspected presence of vasculitis.

h. History of Gilbert's Syndrome.

i. History of malignancy within the past 5 years with the exception of specific cancers that are cured by surgical resection (e.g., skin cancer), subjects under evaluation for possible malignancy are not eligible.

2. History of/sensitivity to GSK3389404 or components thereof or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

3. Confirmed or suspected HCC as evidenced by:

   a. Alpha-fetoprotein concentration ≥200 ng/mL. If the screening alpha-fetoprotein concentration is ≥50 ng/mL and <200 ng/mL, the absence of liver mass must be documented by imaging within 6 months before randomization.

4. Liver cirrhosis or evidence of cirrhosis as determined by any of the following:

   a. Positive liver biopsy (i.e., Metavir Score F4) within 12 months of screening

   b. Fibroscan >12 kPa within 12 months of screening

   c. Aspartate aminotransferase (AST)-Platelet Index (APRI) >2 and FibroSure result >0.7 within 12 months of screening

   d. Investigator judgement

   For subjects without a test for cirrhosis in the above timeframes, APRI and FibroSure should be performed during the screening period to rule out cirrhosis.

5. Hepatitis C virus (HCV) co-infection

6. Human immunodeficiency virus (HIV) co-infection

7. Hepatitis D virus (HDV) co-infection

8. Laboratory results as follows:

   a. Total bilirubin concentration >1.25 X ULN

   b. Serum albumin concentration <3.5 g/dL

   c. International normalized ratio (INR) >1.25

   d. Platelet count <140 X 10^9/L

   e. Serum creatinine concentration greater than the ULN

   f. Glomerular filtration rate (GFR) <90 mL/min as calculated by the Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) formula.

      Subjects with GFR <90 mL/min but ≥60 mL/min may be considered after consultation with the GSK medical monitor.

g. Urine albumin to creatinine ratio (ACR) ≥0.03 mg/mg (or ≥ 30 mg/g). In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement

i. In cases where subjects 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 patient does not have a history of diabetes, hypertension or other risk factors that may affect renal function and discuss with the PPD or GSK medical monitor, or designee

9. Positive test for blood in urine. In the event of a positive test, the test may be repeated once, and if repeat is negative or if urine microscopy reveals <5 red blood cells (RBC) per high-power field (HPF), the subject is considered eligible.
10. 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 subject meets exclusion criterion).
11. Currently taking, or took within 3 months of screening, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks) or topical/inhaled steroid use.
12. Current alcohol use as judged by investigator to potentially interfere with participant compliance.
13. A positive pre-study treatment screen and an unwillingness to refrain from use of illicit drugs (or substances with abuse potential) and adhere to other protocol-stated restrictions while participating in the study. [The screen refers to illicit drugs and substances with abuse potential. Medications that are used by the patient as directed, whether over-the-counter or through prescription, are acceptable and would not meet the exclusion criteria]
14. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
15. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives (if known) or twice the duration (if known) of the biological effect of the study treatment (whichever is longer) or 90 days (if half-life or duration is unknown).
16. Prior treatment with any non-GSK oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing day or prior treatment with GSK oligonucleotide within 3 months prior to the first dosing day.
17. Pregnant or lactating females at screening and prior to dosing

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT)

publishing requirements, and respond to queries from regulatory authorities, a minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and SAEs (see Section 7.3.1.5).

5.4. Withdrawal/Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. Subjects who are discontinued from study treatment will enter the post-treatment follow-up period (please submit an electronic protocol inquiry platform [EPIP] query (either site or clinical research associate [CRA] may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment) unless consent is withdrawn. Every effort should be made to complete the early termination (ET) study procedures and observations if the subject does not enter post-treatment follow-up.

For a subject who fails to attend the study site for a required study visit, the following actions must be taken:

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

Subjects are not obligated to state the reason for withdrawal, but the investigator must make every attempt to elucidate a reason. The efforts must be documented in the source including efforts to locate a subject that has been deemed lost to follow-up. The reasons for withdrawal, or failure to provide a reason, must be documented in the case report form (CRF). If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

All subjects who discontinue prematurely from the study will be asked for additional information to establish the reason for withdrawal. Reasons for study withdrawal may include:

- Adverse event
- Subject meets stopping criteria (as outlined in Section 5.4.1, Section 5.4.2, Section 5.4.3, Section 5.4.4, and Section 5.4.5)
- Protocol deviation

- Pregnancy
- Non-compliance
- Subject lost to follow-up
- Subject withdraws consent
- Investigator discretion
- Sponsor terminates the study

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

Subjects who are withdrawn from the study may be replaced as follows:

- In Part 1, a subject may be replaced if he/she does not complete the study through Day 3.
  - Replacement subjects will receive the same study treatment as the withdrawn subject.
- In Part 2, subjects that withdraw from the study will not be replaced.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study treatment and the follow-up period.

Table 5 provides guidance for liver stopping criteria for subjects with baseline ALT less than or equal to the ULN and for subjects with elevated baseline ALT.

Eligible subjects in Part 1 and Part 2 may have an elevated ALT at screening as specified in Section 5.1. However, the screening ALT may differ from the baseline ALT. Baseline ALT will be measured prior to dosing on Day 1, but results will not be available from the laboratory until after the subject has already been dosed.

A CHB subject who meets the criteria listed in Table 5 will be permanently discontinued from study treatment. Every attempt must be made to have the subject return to the study site (within 24 hours) for repeat liver chemistries, additional testing, and close monitoring (a specialist or hepatology consultation is recommended). The event must be reported to GSK/designee within 24 hours of learning of its occurrence. Subjects must be monitored twice weekly until liver chemistries (ALT, AST, alkaline phosphatase [ALK], bilirubin) resolve, stabilize, or return to within baseline (Day 1 pre-dose) values. Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment.

Refer to Appendix 2 (Section 12.2) for details of the required assessments if a subject meets any of the liver chemistry stopping criteria.

Subjects with ALT ≥3 X baseline or ≥3 X ULN (if baseline ALT ≤ULN) and who do not meet the stopping criteria outlined in Table 5 can continue with the study treatment. At any point, if these subjects meet the liver chemistry threshold stopping criteria or are unable to return for weekly liver chemistries, study treatment must be permanently stopped, additional testing performed, and the subject will continue safety follow-up procedures until liver chemistries resolve, stabilize, or return to baseline (Day 1 pre-dose) values. The subject must then attend the Follow-up visits specified in the Time and Events Table (Section 7.1).

Subjects who meet the stopping criteria with ALT but do not meet bilirubin stopping criteria must be immediately discontinued from study treatment. Every attempt must be made to have the subject return to clinic within 24 to 72 hours for repeat liver chemistries and additional testing and weekly monitoring until liver chemistries (ALT, AST, ALK, bilirubin) resolve, stabilize, or return to within baseline (Day 1 pre-dose) values. This event must be reported to GSK/designee within 24 hours of learning of its occurrence. Upon completion of the safety follow-up procedures, the subject must attend the Follow-up visits specified in the Time and Events Table (Section 7.1).

Table 5 Liver Stopping Criteria

	Baseline Bilirubin ≤ULN	**Baseline Bilirubin >ULN**
Baseline ALT ≤ULN	If ALT ≥5 X ULN, permanently withdraw study treatment	If ALT ≥5 X ULN, permanently withdraw study treatment
	If ALT ≥3 to <5 X ULN, permanently withdraw study treatment if any of the following apply: • associated with the appearance or worsening of hepatitis symptoms • bilirubin ≥1.5 X ULN (>35% direct) • increase persists ≥4 weeks	If ALT ≥3 to <5 X ULN, permanently withdraw study treatment if any of the following apply: • associated with the appearance or worsening of hepatitis symptoms • bilirubin ≥1.5 X baseline (>35% direct) • increase persists ≥4 weeks
Baseline ALT >ULN	If ALT ≥5 X baseline or ≥20 X ULN, permanently withdraw study treatment.	If ALT ≥5 X baseline or ≥20 X ULN, permanently withdraw study treatment.
	If ALT ≥3 to <5 X baseline (up to <20 X ULN), permanently withdraw study treatment if any of the following apply: • associated with the appearance or worsening of hepatitis symptoms • bilirubin ≥1.5 X ULN (>35% direct) • increase persists ≥4 weeks	If ALT ≥3 to <5 X baseline (up to <20 X ULN), permanently withdraw study treatment if any of the following apply: • associated with the appearance or worsening of hepatitis symptoms • bilirubin ≥1.5 X baseline (>35% direct) • increase persists ≥4 weeks

ALT = alanine aminotransferase, ULN = upper limit of normal

Notes:

- Any abnormal laboratory parameters that meet the criteria for individual treatment stop must be confirmed by retest of a new collection of blood samples as soon as possible.
- Any deterioration from the baseline in the liver parameters must be confirmed by retesting ALT, total bilirubin, and direct bilirubin.
- If 1 criterion in the list above is met and confirmed by retesting, further treatment may be stopped for the subject after discussion with the medical monitor. Results of retesting must be evaluated before the next dose is administered.

5.4.1.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- For Part 1 and Part 2 of this study, QTcF will be used to determine eligibility for and discontinuation from study treatment.
- A subject who meets either of the bulleted criteria below will be discontinued from study treatment:
  - QTcF >500 msec
  - Change from baseline in QTcF >60 msec

Discontinuation of subjects will be based on average QTcF from triplicate ECGs. If a single ECG measurement demonstrates a prolonged QTcF interval, the ECG should be repeated 2 more times and the average of the 3 QTcF values used to determine whether the subject should be discontinued from the study treatment.

Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment

5.4.3. Hematological Stopping Criteria

In Parts 1 and 2, a subject who meets any of the criteria below will be discontinued from study treatment:

- Hemoglobin ≤9.9 g/dL
- Absolute neutrophil count (ANC) ≤750/mm^3
- Platelets ≤75 X 10^9/L

Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment

5.4.4. Renal Function Stopping Criteria

If any of the following are observed in Part 1 or Part 2, results should be confirmed**,** and if confirmed, further evaluation for alternative causes should be pursued in consultation with the medical monitor:

- Persistent urine ACR ≥0.03 mg/mg (≥ 30 mg/g) and without alternative cause(s) identified
- Blood in urinalysis ≥5 RBC per HPF confirmed by microscopy without alternative cause(s) identified
- Persistent elevation of serum creatinine (>26.52 μmol/L change from baseline) without an alternative cause identified

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 creatinine, serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP), and/or complement panel (C3, C4, C5a and Bb). Further evaluation and actions should be determined by the investigator in consultation with the medical monitor.

5.4.5. Pharmacokinetic Stopping Criteria

Part 1: Doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma $AUC_{(0-\infty)}$ and C_{max} observed at the NOAEL dose of 30 mg/kg/week in the 13-week monkey toxicity study ($AUC_{(0-\infty)}$ = 492.7 mg•h/mL and C_{max} = 52.7 mg/mL).

A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 492.7 mg•h/mL and 52.7 mg /mL (mean exposures at NOAEL in the 13-week monkey study), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection. Dose escalation may be stopped or a smaller dose increment selected (Section 6.3) for the next cohort if the predictive probability of exceeding the mean NOAEL exposure is greater than 50%.

Part 2: No interim PK analysis is planned.

5.5. Subject and Study Completion

- A completed subject in Part 1 is one who has completed Day 60 visit. An ongoing subject who misses the Day 60 visit will be considered as lost to follow-up.
- A completed subject in Part 2 is one who has completed Day 169 visit. An ongoing subject who misses the Day 169 visit will be considered as lost to follow up.
- For subjects who participate in the optional extended post treatment follow-up period, a completed subject in extended follow-up period is one who has completed the Day 450 visit. An ongoing subject who misses the Day 450 visit will be considered as lost to follow up for the optional extended follow-up period.

The study will be completed after all subjects complete the last study visit or are considered lost to follow-up.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to GSK3389404 or placebo or both. Details of the study treatment are provided in Table 6.

Table 6 Study Treatment

Study Treatment		
Product Name:	GSK3389404	Placebo
Formulation Description:	Clear colorless to slightly yellow solution	Clear colorless solution
Dosage Form:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	100 mg/mL; 1.0 mL nominal volume per vial (minimal overfill per vial)	Placebo
Route/Administration/Duration:	SC, single and multiple (once weekly, bi-weekly, up to 85 days)	SC, single and multiple (once weekly, bi-weekly, up to 85 days)
Dosing Instructions:	Administer SC	Administer SC
Manufacturer/Source of Procurement:	GSK Global Manufacturing and Supply, Parma (Italy)	Locally sourced normal saline
Method for Individualizing Dosage:	Dispensing into syringes	Dispensing into syringes

GSK = GlaxoSmithKline, SC = subcutaneous

Dosing volumes are presented in Table 7. Study treatment administration will take place after completion of all pre-dose study assessments as specified in the Time and Events Tables (Section 7.1). The site of injection will be recorded for each subject and dose. Sites of injection are listed in order of preference and are a guide for the clinical staff. Injections may be rotated within each anatomical site. Injection into areas with ongoing injection site reactions (ISRs) should be avoided.

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

Please refer to the Study Reference Manual (SRM) provided by the Sponsor or designee for more information about study treatment administration.

Table 7 Study Treatment Dose and Injection Volume

Dose[1]	**Volume to Administer**[2]
30 mg or placebo	0.30 mL
60 mg or placebo	0.60 mL
120 mg or placebo	1.2 mL

1. Dose may change based on safety and pharmacokinetic data from preceding cohort(s)
2. If a change in dose is warranted, volume to administer (mL) = dose (mg)/100

6.2. Treatment Assignment

Separate randomization schedules will be generated for each part of the study. The randomization schedule for the optional Japanese Part 2 sub-study will be generated separately. The randomization schedules will be generated by an independent randomization team within the clinical research organization (CRO) biostatistics department. The randomization schedule will be generated using SAS codes developed by a CRO technical team.

Subjects in Part 1 will be assigned to a dosing cohort based on the order in which they are enrolled. Within each cohort, subjects will be randomly assigned to study treatment (GSK3389404:placebo [3:1]) in accordance with the randomization schedule generated before the start of the study. As discussed in Section 5.4, subjects that withdraw from Part 1 of the study may be replaced. The new subject will be assigned a replacement randomization number to receive the same study treatment as the subject being replaced.

Two randomization schedules for Part 2 will be generated after dosing in Part 1 is completed and dose levels and regimens for Part 2 have been identified. A separate randomization schedule will be generated for the sentinel group. The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo.

Subjects in Part 2 will be randomized in a 1:1 ratio (active:placebo) in the sentinel group. Remainder of the Part 2 subjects will be randomized in an approximately 10:1 ratio (active:placebo). The overall randomization ratio of Part 2 will be an approximately 11:2 ratio (active:placebo). The randomization ratio of the optional Japanese Part 2 sub-study will be provided in a Japan country-specific protocol amendment/supplement.

	Sentinel		Remainder	
Part 2	**Active**	**Placebo**	**Active**	**Placebo**
60 mg GSK3389404 weekly	1	1	10	1
120 mg GSK3389404 bi-weekly	1	1	10	1
120 mg GSK3389404 weekly	1	1	10	1

Study site personnel will be required to contact the central randomization service for assignment of a unique identifier (designating the subject's randomization code) for each subject participating in the study. A unique treatment number will be assigned for each subject participating in the study.

6.3. Planned Dose Adjustments

This protocol allows some alteration from the currently outlined dosing plan for Part 1.

- In Part 1, the decision to proceed to the next dose level of GSK3389404, to adjust the next dose level, or add/remove cohorts will be made by the Dose Escalation Committee (Section 10.8.1) based on safety, tolerability and preliminary PK

and/or PD data through Day 3 obtained in at least 3 subjects that received GSK3389404 at the prior dose level.

- Dose adjustments may involve either an increase or a decrease in the planned dose. However, the maximum dose will not exceed 240 mg and the maximum exposure will not exceed the monkey mean NOAEL exposures observed in the 13-week monkey toxicity study.
- A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 492.7 µg•h/mL and 52.7 µg/mL (mean exposures at NOAELof the 13-week monkey study at steady state), respectively, may be calculated with adequate data for the next dose levels and used together with safety and tolerability data to aid next dose selection.
- In the case of undetectable or extremely low concentrations following the first dose (e.g., if the majority of PK samples are below LLOQ), a more than 3-fold increase in dose may be considered for the next dose level.
- The dosing plan may also be adjusted to expand a dosing cohort (enroll additional subjects) to further evaluate safety, PK, and/or PD findings at a given dose level, or to add cohort(s) to evaluate additional dose level(s), not exceeding the maximum dose as defined in Section 4.1. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.
- Planned cohorts may be removed depending on safety, tolerability, PK, and/or PD results from the previous cohorts as follows:
  - If AEs, which are of Grade 3 or Grade 4 severity as defined within the Division of Acquired Immune Deficiency Syndrome (DAIDS) table in Appendix 3 (Section 12.3) and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK3389404 are observed in more than 40% of the subjects in a group, the dose escalation will be temporarily halted, and no further subject will be administered until a full safety review of the study has taken place. Relevant reporting and discussion with the medical monitor, relevant GSK personnel, and with the Independent Ethics Committee (IEC) will then take place prior to any resumption of dosing.
  - If the same SAE (i.e., similar SAE term) occurs in more than one subject, the dose escalation will be temporarily halted, and no further subject will be administered until a full safety review of the data has taken place. Relevant reporting and discussion with the medical monitor, relevant GSK personnel, and with the IEC will then take place prior to any resumption of dosing.

- The above criteria will apply even if measured PK parameters are below the above-mentioned PK stopping criteria, and every effort will be made to take a blood sample at the time of the event for PK analysis in the presence of any of the above events.

This protocol allows some alteration from the currently outlined dosing plan for Part 2.

- After review of Part 1 data, adjustments may be implemented for the planned duration of multiple dose administration in Part 2.
- In Part 2, if multiple treatment arms show similar efficacy and safety profiles, additional Part(s) may be added to the study protocol via a protocol amendment to allow for further evaluation.

6.4. Subject Specific Dose Adjustment Criteria

Subject specific dose adjustment criteria will not be implemented in this study. Study treatment restart or rechallenge after the stopping criteria are met by any subject participating in this study is not allowed.

6.5. Blinding

This will be a double-blind (sponsor unblinded for Part 1) study and the following will apply.

- Study subjects and study site staff (other than unblinded pharmacy personnel) will be blinded to study treatment assignment.
- The GSK study team will be unblinded at the aggregate level for decision making for Part 1 of the study. Where possible, GSK personnel will not have access to subject specific treatment assignment so as to not potentially introduce bias in discussions with the study site(s). The pharmacokineticist, statisticians, programmers and data managers, however, may need access to subject randomization during the course of the study for analysis purposes to support dose adjustment and escalations in Part 1. Other GSK/CRO staff may be included in discussions around dose adjustments and progression if it is deemed necessary and relevant by the above mentioned GSK/CRO study team members.
- In Part 2, dosing regimens will not be blinded. It may also be difficult to blind dose levels. For example, subjects randomized to a total monthly dose of 240 mg in a monthly dosing regimen, will be given two injections each with 120 mg; whereas subjects randomized to other active treatment groups will receive only one injection in a visit. Dose levels may also be identified by the dosing volume. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered similarly to the corresponding active treatment group. Therefore, the dose level and dosing regimen of a subject will be known; however, it will be unknown if a subject is receiving an active treatment at each dose level or placebo. Thus, the double-blind nature of Part 2 will be maintained.
- Senior management review of unblinded efficacy data is planned for both parts of the study (this includes the Japanese optional sub-study). For Part 1, the review provides early information on potential efficacious dose and dose frequency including the need for dose escalation. For Part 2, the review will facilitate internal governance decision making on project progress and trigger further studies

- The frequency of management review in Part 2 will be synchronized with monthly blinded SRT review of the study as appropriate. The management review of the Part 2 data will occur as required for decision making.
- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
    - It is preferred (but not required) that the investigator first contacts the medical monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
    - If the medical monitor or appropriate GSK personnel are not contacted before the unblinding, the investigator must notify the medical monitor or appropriate GSK personnel as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
    - The date and reason for the unblinding must be fully documented in the CRF

A subject may continue in the study if that subject's treatment assignment is unblinded. The primary reason for the unblinding (the event or condition which led to the unblinding) will be recorded in the CRF.

GlaxoSmithKline's GCSP staff may unblind the treatment assignment for any subject 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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

GSK3389404 solution for injection 100 mg/mL is available in a single use 3-mL stoppered Type 1 glass vial containing an aliquot of the modified phosphorothioate oligonucleotide dissolved in a phosphate buffer. The vial contains a minimal overfill to allow a single 1.0 mL withdraw volume. The contents of the label will be in accordance with all applicable regulatory requirements.

A placebo to match GSK3389404 solution for injection will be locally sourced normal saline solution.

6.7. Preparation/Handling/Storage/Accountability

The unblinded pharmacist, or qualified designee, will prepare GSK3389404 and placebo for SC injection from bulk supply according to the central randomization schedule. The preparation of each dose will be confirmed by a second member of the unblinded pharmacy staff. Please refer to the SRM provided by the sponsor or designee for more detailed instructions for study treatment preparation.

- Upon receipt, the investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are to be reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment 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) or 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.

6.8. Compliance with Study Treatment Administration

All subjects will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.9. Treatment of Study Treatment Overdose

For this study, any dose of GSK3389404 greater than the subject's randomized treatment assignment will be considered an overdose.

There is no specific antidote for overdose with GSK3389404. In the event of a suspected overdose, the investigator should do the following:

1. Contact the medical monitor immediately.
2. Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK3389404 can no longer be detected systemically (at least 5 half-lives for GSK3389404).

3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

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

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Meals and Dietary Restrictions

Admission to the study site is optional. If subjects opt to stay in-house in Part 1, subjects will be restricted to meals and beverages provided at the study site.

- On Day 1, a snack (not full meal) will be provided after dosing and completion of study procedures. A meal or lunch will be provided approximately 4 hours post-dose. If appropriate, dinner will be provided approximately 9 hours post-dose and an evening snack may be available until 22:00 hours.
- On Day 2, breakfast, lunch, and dinner may be provided.
    - Subjects may be discharged at any time on Day 2.
    - An evening snack may be available until 22:00 hours.
- On Day 3, subjects who decide to stay in-house through Day 3 will be offered a meal (e.g., bagged or canteen) after completion of morning procedures/prior to discharge from the study site.

During Part 2 (and Part 1 outpatient visits), subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures at each outpatient visit.

6.11.2. Alcohol and Tobacco

- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final PK and or PD sample during each session.
- Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the study site.

6.11.3. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. For the duration of the study, until final follow-up (this includes the optional additional follow-up period), subjects are encouraged to refrain from changing their activity beyond that which they normally perform. While domiciled in the study site, subjects may participate in light recreational activities.

6.12. Concomitant Medications and Non-Drug Therapies

All medications taken at any time from 3 months prior to Baseline (Day 1 pre-dose) to the final Follow-up visit (this includes the optional additional follow-up period) will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

6.12.1. Permitted Medications and Non-Drug Therapies

In Part 1, permitted medication includes nucleos(t)ide agents such as tenofovir, entecavir, lamivudine, adefovir and telbivudine. Treatment naïve patients should avoid initiating HBV therapy until completion of the final follow-up visit unless deemed medically necessary by the investigator.

In Part 2, required medication includes nucleos(t)ide agents such as tenofovir, entecavir, lamivudine, adefovir and telbivudine.

If patients are receiving nucleos(t)ide therapy, administration of the nucleos(t)ide should continue unchanged unless directed by the physician. There are no requirements with regards to the timing of the administration of nucleos(t)ide agent in relation to the study medicine.

Other concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 6.12.2).

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

6.12.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications are not permitted during Part 1 and Part 2 (until Day 169 unless indicated otherwise):

- PEG-interferon or other immunomodulating therapies
- Immunosuppressing drug (e.g., prednisone) use >2 weeks duration from 3 months prior to Screening through the final Follow-up visit (see Exclusion Criterion 11, Section 5.2).

- Non-GSK -oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit or prior treatment with a GSK oligonucleotide from 3 months prior to Day 1 through the final Follow-up visit (includes optional follow-up period if applicable; see Exclusion Criterion 16, Section 5.2).

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is specified in the Time and Events Tables in Section 7.1. Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables, are essential and required for study conduct.

The following points must be noted:

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.

The timing and number of planned study assessments, including safety, PK, or PD assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

The IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

No more than 500 mL of blood will be collected over a 56-day period, including any extra assessments that may be required.

7.1. Time and Events Tables

Screening assessments are detailed in Table 8 for Part 1 and Part 2 of the study.

Part 1 assessments are detailed in Table 9 (Day -1 and Day 1) and Table 10 (Day 2 to Day 60/ET).

Part 2 assessments are provided in different tables based on dosing regimen.

- Once weekly dosing regimen assessments are detailed for the treatment period in Table 11 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 12 (Day 92 to Day 169/ET, with an optional additional follow-up on Days 270, 360, and 450).

- Bi-weekly dosing regimen assessments are detailed for the treatment period in Table 13 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 14 (Day 92 to Day 169/ET, with an optional additional follow-up on Days 270, 360, and 450).

Table 8 Time and Events Table: Screening: Single Ascending Dose (Part 1) and Multiple Dose (Part 2)

Assessment	**Screening (Up to 30 days Prior to Day 1)***
Informed Consent (obtained any time prior to screening)	X
Inclusion and exclusion criteria	X
Demography	X
Medical history (includes substance usage[1]) and current medical conditions	X
Safety Assessments	
Medication history and concomitant medication review	X
Full physical exam including height and weight	X
Vital signs[2]	X
12-lead ECG[3]	X
Laboratory Assessments	
Drug/Alcohol screen	X
Serum hCG pregnancy test (as appropriate)	X
FSH/Estradiol (as appropriate)	X
Hematology/Chemistry/Urinalysis[4]	X
Urine ACR[5]	X
PT, INR, aPTT	X
HIV and hepatitis C screen	X
Hepatitis B screen (HBsAg; plasma or serum)	X
Hepatitis B profile (HBV DNA, HBeAg; plasma or serum)	X
Hepatitis D screen	X
Alpha-fetoprotein (as appropriate)[6]	X
Test of cirrhosis (as appropriate)[7]	X

ACR = albumin to creatinine ratio, aPTT = activated partial thromboplastin time, ECG = electrocardiogram, FSH = follicle-stimulating hormone, HBeAg = hepatitis B virus e-antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, hCG = human chorionic gonadotropin, HIV = human immunodeficiency virus, INR = international normalized ratio, PT = prothrombin time

* Eligible subjects who exceed the regular 30-day screening window by 15 days (total 45 days) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility

1. Drugs, alcohol, and tobacco.
2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
3. 12-lead ECGs (single measurement after 5 minutes of rest in the semi-supine or supine position).
4. Fasting not required for Screening visit.
5. Urine ACR at screening is not required to be first morning void. Subjects will be given a clean urine collection cup to take home and bring back to study site with first morning void, if required for a second measurement.
6. For subjects with confirmed or suspected hepatocellular carcinoma.
7. Test of cirrhosis (Fibroscan or APRI and FibroSure per exclusion criterion 4 in Section 5.2). For subjects without a test for cirrhosis in the specified timeframes, APRI and FibroSure should be performed during the screening period to rule out cirrhosis.

Table 9 Time and Events Table: Day -1 and Day 1 of Single Ascending Dose (Part 1)

Assessments	Day -1	Day 1									
				Post Dose in Hours (h)							
		Pre-dose[2]	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h
Inclusion and exclusion criteria		X									
Admission to study site[1]	(X)	(X)									
Discharge from study site[1]											(X)
Randomization[2]		X									
Study treatment dosing[3]			X								
Meals[4]									X		
Safety Assessments											
AE/SAE review[5]	← Continuous →										
Concomitant medication review	← Continuous →										
Brief physical exam		X									
Vital signs[6]		X			X		X		X		X
12-lead ECG[7]		X					X		X		X
Injection site reactions[8]			X	X	X	X	X	X	X	X	X
Laboratory Assessments											
Pregnancy test (as appropriate)[9]		X									
Hematology/Chemistry/Urinalysis [10,11]		X									
Urine ACR[11,12]		X									
Complement (C3/C4)		X					X		X		X
PT, INR, aPTT		X					X		X		X
hs-CRP		X									
PK sampling[13]		X		X	X	X	X	X	X	X	X
Archived serum and plasma samples[14]		X									
HBsAg and HBV DNA		X									X
HBeAg[15]		X									X
HBV genotype/phenotype[16]		X									X

ACR = albumin to creatinine ratio;, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, HBeAg = hepatitis B virus e-antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, hCG: human chorionic gonadotropin, HIV = human immunodeficiency virus, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, ISR = injection site reaction, PK = pharmacokinetics, PT = prothrombin time

1. Admission to the study site is optional. Subjects admitted on Day -1 may be discharged after completion of all protocol specified procedures on Day 1, 8-hour time point, with instructions to return for outpatient visits (Days 3, 8, 15, 22, 30, and 60).
2. Subjects randomized to GSK3389404 or placebo on Day 1 prior to dosing.
3. Study treatment will be administered as subcutaneous injection(s) subsequent to laboratory assessments prior to dosing.
4. On Day 1, subjects may receive a snack (not full meal) after completion of study procedures and post-dose.. A meal or lunch will be approximately 4 hours (±1 hour) dosing. If appropriate, dinner will be provided approximately 9 hours (±1 hour) after dosing. An evening snack (optional) may be provided until 22:00 hours.
5. Adverse events will be collected from the first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
6. Temperature, respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
7. 12-lead ECGs will be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and single measurements at all other time points.
8. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
9. Female subjects at screening: serum hCG pregnancy test; all other time points: serum hCG or urine pregnancy test. (Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)
10. Sample must be obtained prior to dosing.
11. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
12. Collect first morning urine void sample for ACR assessment. Subjects may be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their visit.
13. Plasma PK samples to be collected pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible). Post-dose PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.
14. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
15. HBeAg-positive subjects only.
16. HBV genotype/phenotype sample to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

Table 10 Time and Events Table: Day 2 to Day 60 of Single Ascending Dose (Part 1)

	Day 2	DAY 3	Day 8	Day 15	Day 22	Day 30	Day 60	
	Post Dose in Hours (h)		(±1 day)	(±1 day)	(±1 day)	(±1 day)	(±1 day)	ET
Assessment		48 h (±8 h)						
Meals[1]	(X)[1]	(X)[1]						
Discharge from study site[2]	(X)	(X)						
Outpatient visits		(X)	X	X	X	X	X	X
Safety Assessments								
AE/SAE review[3]	← Continuous →							
Concomitant medication review	← Continuous →							
Brief physical exam			X			X	X	X
Vital signs[4]		X	X			X		X
12-lead ECG[5]		X	X			X		X
Injection site reactions[6]		X	X	X	X	X	X	X
Laboratory Assessments[7]								
Pregnancy test (as appropriate) [8]			X			X	X	X
Hematology/Chemistry/Urinalysis[9]		X	X			X	X	X
Urine ACR[9,10]			X			X	X	X
Complement (C3/C4)		X	X			X		X
PT, INR, aPTT		X	X			X		X
hs-CRP		X	X			X		X
PK sampling[11]		X	X			X		X
Archived serum and plasma samples[12]		X	X			X		X
HBsAg, HBV DNA		X	X	X	X	X	X	X
HBeAg[13]		X	X	X	X	X	X	X
HBV genotype/phenotype[14]		X	X	X	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, ET = early termination, HBeAg = hepatitis B virus e-antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

1. On Day 2, breakfast, lunch, and dinner may be provided. If subjects choose to stay in-house through Day 3, then on Day 2, lunch will also be served approximately 4 hours (±1 hour) after the breakfast, dinner will be served approximately 9 hours (±1 hour) after the breakfast, and an evening snack (optional) may be provided until 22:00 hours. If subjects choose to stay in-house through Day 3, they will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures and prior to discharge on Day 3.
2. Subjects may be discharged at any time on Day 2 with instructions to return for outpatient visits (Days 3. 8, 15, 22, 30, and 60). If subjects prefer, they may stay in-house until all Day 3 assessments are completed.
3. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
4. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
5. Single 12-lead ECGs will be measured after 5 minutes of rest in the semi-supine or supine position.
6. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
7. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments
8. Female subjects: serum hCG or urine pregnancy test.
9. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
10. Collect first morning urine void sample for ACR assessment while subjects are in study site. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
11. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.
12. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
13. HBeAg-positive subjects only.
14. HBV genotype/phenotype sample to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

Table 11 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Weekly Dosing

	Treatment Period												
Assessment	**Day 1**	**Day 8 (±2 day)**	**Day 15 (±2 day)**	**Day 22 (±2 day)**	**Day 29 (±2 day)**	**Day 36 (±2 day)**	**Day 43 (±2 day)**	**Day 50 (±2 day)**	**Day 57 (±2 day)**	**Day 64 (±2 day)**	**Day 71 (±2 day)**	**Day 78 (±2 day)**	**Day 85 (±2 day)**
Outpatient visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[1]	X												
Study treatment dosing[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments													
AE/SAE review[3]	← Continuous →												
Concomitant medication review	← Continuous →												
Brief physical exam	X				X				X				X
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[5]	X				X				X				X
Injection site reactions[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[7]													
Pregnancy test (as appropriate)[8]	X				X				X				X
Hematology/Chemistry/ Urinalysis[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR[9,10]	X		X		X		X		X		X		X
Complement (C3/C4)	X		X		X		X		X		X		X
PT, INR, aPTT	X		X		X		X		X		X		X
hs-CRP	X		X		X		X		X		X		X
PK sampling[11]	X[11]				X[11]				X[11]				
Archived serum and plasma samples[12]	X				X				X				X
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg[13]	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotype/phenotype[14]	X		X		X		X		X		X		X
HBsAb	X												X
Meal[15]	X	X	X	X	X	X	X	X	X	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

Note: Except where indicated, assessments are to be conducted pre-dose.

1. Subjects randomized to GSK3389404 or placebo on Day 1 prior to dosing.
2. Study treatment will be administered as subcutaneous injection(s) subsequent to the laboratory collection and other study assessments conducted prior to dosing.
3. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
4. Temperature, respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and single measurements at all other time points.
6. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
7. Samples for clinical laboratory tests to be collected prior to dosing (if applicable).
8. Female subjects at screening: serum hCG pregnancy test; all other time points for females of reproductive potential: serum hCG or urine pregnancy test. (Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)
9. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
10. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
11. On extended PK/dosing days (Days 1, 29, and 57), PK samples will be collected pre-dose (within 15 to 120 minutes prior to dosing; prefer sample as close to pre-dose time point as possible) and at 1, 2, and 3 hours post-dose. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded. PK sampling for the optional Japanese Part 2 sub-study may be detailed in the Japan country-specific protocol amendment/supplement.
12. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
13. HBeAg-positive subjects only.
14. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
15. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Table 12 Time and Events Table: Day 92 to Day 169 of Multiple Dose (Part 2) Once Weekly Dosing

	Post-treatment Follow-up					
Assessment	**Day 92(±2 days)**	**Day 99 (±2 days)**	**Day 113 (±2 days)**	**Day 141 (±2 days)**	**Day 169 Follow-up (±2 days)**	**ET**
Outpatient visit	X	X	X	X	X	X
Safety assessments						
AE/SAE review[1]	← Continuous →					X
Concomitant medication review	← Continuous →					X
Brief physical exam	X	X	X	X	X	X
Vital signs[2]	X	X	X	X	X	X
12-lead ECG[3]					X	X
Injection site reactions[4]	X	X	X	X	X	X
Laboratory assessments[5]						
Pregnancy test (as appropriate)[6]			X	X	X	X
Hematology/Chemistry/Urinalysis[7]	X	X	X	X	X	X
Urine ACR[7,8]	X	X	X	X	X	X
Complement (C3/C4)	X	X	X	X	X	X
PT, INR, aPTT	X	X	X	X	X	X
hs-CRP	X	X	X	X	X	X
PK sampling[9]					X	X
Archived serum and plasma samples[10]	X		X		X	X
HBsAg and HBV DNA	X	X	X	X	X	X
HBeAg[11]	X	X	X	X	X	X
HBV genotype/phenotype[12]		X	X	X	X	X
HBsAb					X	X
Meal[13]	X	X	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, ET = early termination, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
3. Single 12-lead ECGs will be measured after 5 minutes of rest in the semi-supine or supine position.
4. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
5. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments.
6. Female subjects of reproductive potential: serum hCG or urine pregnancy test.
7. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessment.
8. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
9. On PK days (Day 169 / Early Termination), collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded. PK sampling for the optional Japanese Part 2 sub-study will be detailed in the Japan country-specific protocol amendment/supplement.
10. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
11. HBeAg-positive subjects only.
12. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
13. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Table 13 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Bi-Weekly Dosing

	Treatment Period												
Assessment	**Day 1**	**Day 8 (±2 day)**	**Day 15 (±2 day)**	**Day 22 (±2 day)**	**Day 29 (±2 day)**	**Day 36 (±2 day)**	**Day 43 (±2 day)**	**Day 50 (±2 day)**	**Day 57 (±2 day)**	**Day 64 (±2 day)**	**Day 71 (±2 day)**	**Day 78 (±2 day)**	**Day 85 (±2 day)**
Outpatient visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[1]	X												
Study treatment dosing[2]	X		X		X		X		X		X		
Safety Assessments													
AE/SAE review[3]	←						Continuous						→
Concomitant medication review	←						Continuous						→
Brief physical exam	X				X				X				X
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[5]	X				X				X				X
Injection site reactions[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[7]													
Pregnancy test (as appropriate)[8]	X				X				X				X
Hematology/Chemistry/ Urinalysis[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR[9,10]	X		X		X		X		X		X		X
Complement (C3/C4)	X		X		X		X		X		X		X
PT, INR, aPTT	X		X		X		X		X		X		X
hs-CRP	X		X		X		X		X		X		X
PK sampling[11]	X[11]				X[11]				X[11]				
Archived serum and plasma samples[12]	X				X				X				X
HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg[13]	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotype/phenotype[14]	X		X		X		X		X		X		X
HBsAb	X												X
Meal[15]	X	X	X	X	X	X	X	X	X	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

Note: Except where indicated, assessments are to be conducted pre-dose.

1. Subjects randomized to GSK3389404 or placebo on Day 1 prior to dosing.
2. Study treatment will be administered as subcutaneous injection(s) subsequent to the laboratory collection and other study assessments conducted prior to dosing.
3. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
4. Temperature, respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and single measurements at all other time points.
6. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
7. Samples for clinical laboratory tests to be collected prior to dosing (if applicable).
8. Female subjects at screening: serum hCG pregnancy test; all other time points for females of reproductive potential: serum hCG or urine pregnancy test. (Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)
9. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
10. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
11. On extended PK/dosing days (Days 1, 29, and 57), PK samples will be collected at pre-dose (within 15 to 120 minutes prior to dosing; prefer sample as close to pre-dose time point as possible) and at 1, 2, and 3 hours post-dose. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded. PK sampling for the optional Japanese Part 2 sub-study may be detailed in the Japan country-specific protocol amendment/supplement.
12. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
13. HBeAg-positive subjects only.
14. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
15. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Table 14 Time and Events Table: Day 92 to Day 169 of Multiple Dose (Part 2) Bi-Weekly Dosing

	Post-treatment Follow-up					
Assessment	**Day 92 (±2 days)**	**Day 99 (±2 days)**	**Day 113 (±2 days)**	**Day 141 (±2 days)**	**Day 169 (±2 days)**	**ET**
Outpatient visit	X	X	X	X	X	X
Safety Assessments						
AE/SAE review[1]	← Continuous →					X
Concomitant medication review	← Continuous →					X
Brief physical exam	X	X	X	X	X	X
Vital signs[2]	X	X	X	X	X	X
12-lead ECG[3]					X	X
Injection site reactions[4]	X	X	X	X	X	X
Laboratory Assessments[5]						
Pregnancy test (as appropriate)[6]			X	X	X	X
Hematology/Chemistry/Urinalysis[7]	X	X	X	X	X	X
Urine ACR[7,8]	X	X	X	X	X	X
Complement (C3/C4)	X	X	X	X	X	X
PT, INR, aPTT	X	X	X	X	X	X
hs-CRP	X	X	X	X	X	X
PK sampling[9]					X	X
Archived serum and plasma samples[10]	X		X		X	X
HBsAg and HBV DNA	X	X	X	X	X	X
HBeAg[11]	X	X	X	X	X	X
HBV genotype/phenotype[12]		X	X	X	X	X
HBsAb					X	X
Meal[13]	X	X	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, ET = early termination, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
3. Single 12-lead ECGs will be measured after 5 minutes of rest in the semi-supine or supine position.
4. Subjects will be monitored for pain/tenderness, erythema/redness, induration/swelling, and pruritus. Dermatology consult may be warranted (Section 7.3.4). If injection site reaction is observed, then the reaction should be monitored until resolution or stabilization.
5. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments.
6. Female subjects of reproductive potential: serum hCG or urine pregnancy test.
7. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessment.
8. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
9. On PK days (Day 169 / Early Termination), collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded. PK sampling for the optional Japanese Part 2 sub-study will be detailed in the Japan country-specific protocol amendment/supplement.
10. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
11. HBeAg-positive subjects only.
12. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
13. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Table 15 Time and Events Table: Optional Follow-up Period Day 270 to Day 450 for Once Weekly and Bi-weekly Dosing Assessment

	Day 270 (±7 days)	Day 360 (±7 days)	Day 450 (±7 days)	ET
Outpatient visit	X	X	X	X
Safety Assessments				
AE/SAE review[1]	← Continuous →			X
Concomitant medication review	← Continuous →			X
Laboratory Assessments				
Chemistry	X	X	X	X
PT, INR	X	X	X	X
Archived serum and plasma samples[2]	X	X	X	X
HBsAg and HBV DNA	X	X	X	X
HBeAg[3]	X	X	X	X
HBV genotype/phenotype[4]	X	X	X	X
HBsAb	X	X	X	X
Meal[5]	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, ET = early termination, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
2. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
3. HBeAg-positive subjects only.
4. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
5. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

7.2. Screening and Critical Baseline Assessments

Eligibility criteria must be carefully assessed at the Screening visit and at the Baseline visit. Eligible subjects who fall out of the 30-day screening window may be rescreened at the discretion of the investigator/site.

- Eligible subjects who fall within a 45-day window (15 days out of the 30-day screening window) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility.
- For any other subject who is rescreened, all required screening assessments (Section 7.1, Table 8) should be repeated.

Subjects who screen failed under previous versions of the protocol may be re-screened.

Screening assessments are provided in Table 8.

- Demographic parameters (year of birth, sex, race and ethnicity) will be recorded.
- Medical and medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.
- Procedures conducted as part of the subject's routine clinical management (HBsAg, liver biopsy, Fibroscan, APRI, or FibroSure) and obtained prior to signing of informed consent may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the inclusion/exclusion criteria listed in Section 5.

Baseline assessments are provided in Table 9 for Part 1, and Table 11 and Table 13 for Part 2.

7.3. Safety

Planned time points for all safety assessments are specified in the Time and Events Tables (Section 7.1). 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.

7.3.1. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 12.3). The severity of an AE is graded according to the DAIDS table in Appendix 3 (Section 12.3.5.1).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

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

- Any SAEs, including those assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or

related to a GSK product, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- Adverse events will be collected from the time of first dose of study treatment until the final follow-up contact (Section 7.3.1.3) as specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3 (Section 12.3.6).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating, and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3 (Section 12.3.4 and Section 12.3.5).

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). After the SAE or AE are followed until resolution or stabilization or event is otherwise explained, the subject will enter into the post-treatment follow up. The exact schedule for post-treatment follow up for those subjects who withdraw study treatment early should be confirmed with the GSK team. Further information on follow-up procedures is given in Appendix 3 (Section 12.3.5.4).

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 (Section 12.3.3) and all deaths, whether or not they are considered SAEs, specific cardiovascular 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 cardiovascular CRFs are presented as queries in response to reporting of certain cardiovascular Medical Dictionary for Regulatory Activities (MedDRA) terms. The cardiovascular information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a cardiovascular 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.

7.3.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.

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

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

Females of reproductive potential are permitted in this study. Pregnancy tests will be conducted on all female subjects at the Screening and Baseline visits. A negative pregnancy test result is required to determine eligibility for study treatment administration. Pregnancy testing will also be conducted as specified in the Time and Events Tables (Section 7.1).

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until the final specified Follow-up visit (includes the optional follow-up period for Part 2).

- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 12.4.2).
- Male subjects with female partners who are currently pregnant should comply with the acceptable contraceptive requirement as detailed in the protocol. No precautions are required for the male subject's pregnant partner.

7.3.3. Physical Exams

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

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

7.3.4. Injection Site Reactions

Injection Site Reactions are any experiences which occur at the site of injection of the study treatment. Subjects will be monitored closely for the following in relation to ISRs:

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

Injection site reactions will be graded according to the criteria provided in the DAIDS grading table (see Appendix 3, Section 12.3.5.1).

Digital photographs will be documented where possible on all subjects who have an ISR that meets SAE criteria OR is Grade 3 or above for injection site pain/tenderness, erythema/redness, induration/swelling, or pruritus per the DAIDS grading table (see Appendix 3, Section 12.3.5.1).

Dermatology will be consulted on all subjects who have an ISR that meets SAE criteria OR is Grade 3 or above for injection site pain/tenderness, erythema/redness, induration/swelling, or pruritus per the DAIDS grading table (see Appendix 3, Section 12.3.5.1) or if clinically significant and persistent beyond 14 days. Dermatology may also be consulted for other ISRs if the investigator or GSK medical monitor feels it is medically necessary.

Details regarding photo collection and any other follow-up will be given by the GSK medical monitor at the time of assessment.

7.3.5. Vital Signs

- Vital signs will be measured after 5 minutes of rest in the semi-supine or supine position:
  - Systolic and diastolic blood pressure, heart rate, temperature, and respiration rate will be collected as single measurements.
- 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.

7.3.6. Electrocardiogram

- All ECGs will be collected after 5 minutes of rest in the semi-supine or supine position.
  - All ECGs will be conducted using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
  - Triplicate 12-lead ECGs will be obtained at pre-dose on Day 1. Single 12-lead ECGs will be obtained at all other time points.
- 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.
- Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTcF readings that may be necessary.

7.3.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 16, must be conducted in accordance with the Laboratory Manual and the Time and Events Tables in Section 7.1. Fasting is not required for laboratory testing. Details for blood and urine sampling are provided in a separate Laboratory Manual.

Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples are provided in a separate Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the central laboratory responsible for the assessments.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology laboratory assessments. The results of each test must be entered into the CRF.

- For China, urine drug screen. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time.

Table 16 Protocol Required Safety Laboratory Assessments

Laboratory Assessments[1]	Parameters			
Hematology	Platelet Count		*RBC Indices*:	*WBC count with Differential:*
	RBC Count		MCV	Neutrophils
	Hemoglobin		MCH	Lymphocytes
	Hematocrit			Monocytes
	Reticulocyte count			Eosinophils
				Basophils
Clinical chemistry[2]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total protein
	GFR (CKD-EPI)	Calcium	ALP	Albumin
	Uric acid	Phosphorous	GGT	hs-CRP
	Glucose	Magnesium	CPK	
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Coagulation	• INR • PT • aPTT			
Complement	• C3, C4, C5a, Bb			
Other Screening and/or Follow-up tests	• Urine ACR[3] • HIV, HCV, HDV • HBsAg • HBsAb • HBV DNA • Viral genotype/phenotype • HBeAg • Alpha-fetoprotein (in subjects with confirmed or suspected HCC) • Test of cirrhosis (APRI and FibroSure) performed as needed in subjects without a test in the necessary screening timeframe (exclusion criterion 4 in Section 5.2) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • FSH and estradiol (as needed in women of non-child bearing potential) • Serum hCG pregnancy test at Screening, serum or urine hCG pregnancy test at other time points[4] • HBV RNA, HBcrAg, and/or IDO may be analyzed from archived samples			

ACR = albumin to creatinine ratio, ALP = alkaline phosphatase ALT = alanine aminotransferase, APRI = AST platelet index, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CKD-EPI = Chronic Kidney Disease Epidemiologic Collaboration, CPK = creatine phosphokinase, FSH = follicle-stimulating hormone, GFR = glomerular filtration rate, GGT = gamma glutamyl transpeptidase, HBcrAg = hepatitis B core-related antigen, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HDV = hepatitis D virus, hCG = human chorionic gonadotropin, HIV = human immunodeficiency virus, hsCRP = high sensitivity C-reactive protein, IDO = indoleamine 2,3 dioxygenase, INR = international normalized ratio, MCH = mean corpuscular hemoglobin, MCV = mean cell volume, PT = prothrombin time, RBC = red blood cell

1. Fasting is not required for laboratory testing.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after a liver stopping or monitoring event are given in Section 5.4.1 and Appendix 2 (Section 12.2), respectively.
3. With the exception of the Screening visit, when first morning void is not required, urine ACR assessments will be conducted using the first morning void urine sample. For outpatient visits, subjects will be given a clean urine collection cup for the first morning void on the day of their outpatient visit.
4. With the exception of the Screening visit, local urine testing will be standard for the protocol unless serum testing

is required by local regulation or ethics committee.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for PK analysis of GSK3389404 and ISIS 505358 will be collected at the time points specified in the Time and Events Tables in Section 7.1. The actual date and time of each blood sample collection will be recorded. Since this is the first administration of GSK3389404 to subjects with CHB, the timing of PK samples may be altered and/or additional PK samples may be obtained based on review of safety, tolerability, and PK during the study.

At each PK time point, approximately 4 mL of blood will be collected into potassium ethylenediaminetetraacetic acid (K2 EDTA) tubes. Processing, storage and shipping procedures are provided in the SRM.

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of Platform Technology and Science – InVivo/ InVitro Translation PTS-IVIVT/ Third Party Resources TPR, GSK, the details of which will be included in the SRM. Concentrations of GSK3389404 and ISIS 505358 will be determined from plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once plasma samples have been analyzed for GSK3389404 and ISIS 505358, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-IVIVT/TPR, GSK protocol.

7.5. Efficacy

Blood samples for HBsAg will be collected as specified in the Time and Events Tables in Section 7.1. Blood collection, processing, storage, shipping, and analysis details are provided in the SRM.

7.6. Biomarker(s)/Pharmacodynamic Markers

Blood samples for HBeAg and HBV DNA will be collected as specified in the Time and Events Tables in Section 7.1. Blood collection, processing, storage, shipping, and analysis details are provided in the SRM.

Additional blood samples for archive will be collected as specified in the Time and Events Tables in Section 7.1. The archive samples may be used for the purposes of follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.). The archive samples may also be used for studying biomarkers that may be affected by treatment, such as HBcrAg, HBV RNA or indoleamine 2,3 dioxygenase (IDO). Blood collection, processing, storage, and shipping details are provided in the SRM.

7.7. Viral Genotyping and Phenotyping

Blood samples for HBV viral genotyping and phenotyping will be collected as specified in the Time and Events Tables in Section 7.1. The blood samples will be stored and may be analyzed based on the sponsor's discretion. Blood collection, processing, storage, and shipping details are provided in the SRM.

7.7.1. HBV Resistance Mutation Monitoring

For Part 2, in subjects who are on a stable nucleos(t)ide regimen with adequate suppression of HBV DNA, defined as HBV DNA levels below the LLOQ:

Virologic breakthrough is defined as the occurrence of confirmed virologic breakthrough (e.g., HBV DNA becoming quantifiable after being below the LLOQ).

Plasma or serum HBV DNA levels for each subject will be measured throughout the study (see Time and Events Tables in Section 7.1). If evidence of virologic breakthrough is observed, subjects will be interviewed regarding treatment compliance and the concomitant usage of medication that might affect virus replication (e.g., corticosteroids), and other potentially relevant parameters.

Samples collected for viral genotyping and phenotyping may be used for HBV resistance mutation analysis where the viral genome will be DNA sequenced to determine whether mutations have occurred in the GSK3389404 binding region (and if applicable, whether any known nucleos(t)ide resistance mutations are present in the polymerase coding region).

8. DATA MANAGEMENT

- For this study, subject data will be entered into the CRO data management/capture system, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.
- Case report forms (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

Statistical considerations and planned analyses are summarized in this section. A detailed description of the statistical analyses will be documented in the study Reporting and Analysis Plan (RAP).

9.1. Hypotheses

No formal hypotheses are to be tested in Part 1.

One of the primary objectives of Part 2 of this study is to select the efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint, response rate (RR), based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least a 1.5 times log 10 IU/mL reduction of HBsAg levels from baseline anytime during the study. A model based probability inference approach in Bayesian framework will be used for decision-making as the primary efficacy analysis. An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 90%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥90%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is based on feasibility for Part 1 of this study. No formal calculation of power or sample size for Part 1 of the study will be performed. A sample size of at least 4 HBV subjects (3 receiving active treatment: 1 placebo) in each cohort should provide preliminary estimates of inter subject variability for GSK3389404 PK parameters and initial safety and PD assessments.

In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. There are approximately 11 subjects in each of the active treatment group and approximately 6 subjects in the placebo group. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and dosing regimen. The total sample size will provide sufficient power to select an efficacious treatment group using a Bayesian model based approach sharing common degrees of freedom across treatment arms. With the 3 treatment groups selected for part 2, the probability of declaring success of an inefficacious treatment arm (with RR ≤5%) is less than 14%. On the other hand, if an active treatment arm has a 30% RR, the probability of selecting the treatment arm is about 80% under the model assumption. Appendix 6 (Section 12.6) details the operating characteristics of the design.

9.2.2. Sample Size Sensitivity

Sample size sensitivity and design operating characteristics are detailed in Appendix 6 (Section 12.6).

9.2.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

All Subjects Screened Population

The All Subjects Screened Population will include all subjects who consent to participate in the clinical trial. Subjects in this population will be used for screen failure summary. The population will be defined separately for Part 1 and Part 2.

Safety Population

The Safety Population will include all subjects who receive at least one dose of the study treatment (including placebo) and will be based on the actual treatment received if this differs from that to which the subject was randomized. Subjects in this population will be used for all safety analyses. The population will be defined separately for Part 1 and Part 2.

Pharmacokinetic Population

The PK Population will include all subjects in the Safety population for whom at least one evaluable PK sample will be obtained and analyzed. Pharmacokinetic 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. All PK analyses will be based on this analysis population. The population will be defined separately for Part 1 and Part 2 of the study.

Pharmacodynamic Population

The PD population will include all subjects in the Safety population who provide evaluable PD data. All PD analyses will be based on this analysis population.

Intent-to-Treat Population

The Intent-to-Treat (ITT) population will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for efficacy analyses. Any subject who receives a treatment randomization number will be considered to have been randomized.

9.3.2. Definition of Baseline

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.

9.3.3. Interim Analysis and Final Analysis

Part 1:

No formal interim analysis is planned for Part 1. However, a preliminary PK analysis will be performed after each dose level is completed and the Dose Escalation Committee (Section 10.8.1) will review preliminary safety tolerability, PK and PD data (through Day 3 for at least 3 subjects that received GSK3389404) prior to each dose escalation and prior to initiation of Part 2. Dose escalation can only occur after the Dose Escalation Committee has found that the safety, PK, and PD profiles through Day 3 are supportive to proceed with the evaluation of the next higher dose level.

The relationship between dose levels, plasma GSK3389404 exposure, and associated variability will be characterized by a power model if 3 or more subjects' PK data are available from at least 2 dose levels. The model will be updated as data become available throughout the study. During dose escalation, a Bayesian predictive probability of mean $AUC_{(0-\infty)}$ and C_{max} less than 492.7 µg•h/mL and 52.7 µg /mL (mean exposures at NOAEL of the 13-week monkey study), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid the next dose selection. The Bayesian predictive probability will be based on Whitehead's model [Whitehead, 2001] using non-informative prior for model parameters.

$$y_i = \theta_1 + \theta_2 d_i + \varepsilon_i$$

Where y_i is log-PK of i-th subject, d_i is the log-dose administered to i-th subject. θ_1 and θ_2 are population intercept and slope, respectively and ε_i is random error of i-th subject.

The analysis and reporting of Part 1 may be conducted prior to the completion of Part 2.

Part 2 Interim Analysis:

No formal interim analysis is planned for Part 2.

However, before randomizing all subjects in Part 2, safety data from a sentinel group (1 subject from each treatment group and the corresponding matching placebo) will be reviewed by the GSK internal clinical team or SRT in a blinded manner (Section 10.8.2). Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure (but may include more data) in all subjects in the sentinel group are reviewed. Safety data from all subjects will be reviewed by the GSK internal clinical team or SRT in a blinded manner on a regular basis thereafter.

9.3.3.1. Part 2: Primary Analysis

In Part 2, the primary analysis will be conducted once the last randomized subject in the sentinel group and remainder of subjects have completed the Day 85 visit. Treatment assignment will be unblinded for subjects included in the analysis. The results of this analysis will be used to characterize safety, tolerability and identify efficacious dose and dosing regimen of GSK3889404.

9.3.3.2. Japanese Optional Part 2 Sub-Study Analysis

Details of the analysis of the optional Japanese Part 2 sub-study may be found in the Japan country-specific protocol amendment/supplement. If applicable, the analysis of Japanese cohort will be conducted once the last randomized Japanese subject has completed the Day 85 and/or Day 169 visit. Treatment assignment for the optional Japanese sub-study will be unblinded. Depending on the timing of the last Japanese subject to finish the Day 85 visit, the analysis may or may not be reported together with the Primary analysis.

9.3.3.3. Part 2: 3 month follow up Analysis

The 3 month follow up analysis for Part 2 will be conducted once last randomized subject has completed the Day 169 visit.

9.3.3.4. Part 2: 6 month follow up Analysis

The 6 month follow up analysis for Part 2 may be conducted once last randomized subject has completed the Day 270 visit to support internal decision making and/or regulatory interaction.

9.3.3.5. Part 2: End of Study Analysis

The end of study analysis for Part 2 will be conducted once the last subject participating in the optional follow-up has completed the Day 450 visit.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Safety

Safety and tolerability parameters (AEs/SAEs, physical exams, vital signs, 12-lead ECGs, and clinical laboratory measurements) will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular or graphical formats, as appropriate. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

Adverse events will be coded using MedDRA. Adverse events will be summarized in various subsets, including treatment-emergent AEs (TEAEs) by maximum causality, by

maximum intensity, leading to treatment discontinuation or withdrawal from study, and SAEs.

Exposure to study treatment as the number of doses administered will be presented for each treatment group for Part 2.

Pharmacokinetics

GSK3389404 plasma concentration-time data will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular and graphical formats. GSK3389404 PK parameters will be derived from the concentration-time profiles using WinNonlin. The derived PK parameters, including but not limited to $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, $t_{½}$, and CL/F, will be listed by subject and summarized by treatment group and HBeAg status. Summaries may also combine treatment groups as applicable.

Efficacy

In Part 2, the primary efficacy objective is to select an efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint RR, based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least 1.5 times log 10 IU/mL reduction of HBsAg levels from baseline anytime during the study.

The RR data will be analyzed using a dose-response model. The posterior mean for each active treatment group will be derived from the posterior distribution of the response rates using a 3-parameter logistic regression model using weakly informative priors for model parameters. Estimates for this model's parameters will be derived using the data generated within each treatment arm, i.e., this model will borrow degrees of freedom across active dose levels and regimens therefore providing higher power compared to pair-wise comparisons given the small sample size of each treatment arm.

A Bayesian logistic regression model (BLRM) [Neuenschwander, 2008] is considered to find an efficacious dose in this study.

For dose **d** and regimen **R**, the number of subjects with a response ($\mathbf{Y_{dr}}$) in a treatment arm of size $\mathbf{n_{dr}}$ is binomial. Therefore, $\mathbf{Y_{dr}}| \mathbf{n_{dr}} \sim$ Binomial ($\boldsymbol{\pi_{dr}}$, $\mathbf{n_{dr}}$), with RRs

$$\text{logit}(\pi_{dr}) = \alpha + \beta \log(d/d^*) + \gamma R,$$

where d is the active dose; R is the regimen (R=1 for regimen 1 and R=0 for regimen 2); d* is a reference dose allowing for the interpretation of α as the odds of a response at d*; β is the change in the log-odds of a response by a unit increase in log-dose; γ is the change in the log-odds of a response due to change in regimen. Since this is the first study of administration of GSK3389404 in subjects with CHB, weakly informative priors of the model parameters ($\alpha \sim N(0, \text{var}=100)$, $\beta \sim N(0, \text{var}=25)$, $\gamma \sim N(0, \text{var}=9)$) are assumed. To justify the prior selection, a set of 1000 observations were generated from each of the prior distribution. The estimate of each of the parameters centers close to 0.5, with ranges between (0, 1) and standard deviation approximately 0.5. Posterior distribution of response rates of active treatment arms will be generated using BLRM.

Since it is not expected to have any responder in the placebo arm, posterior distribution of RRs is generated separately from a Beta distribution, i.e., Beta (0.1,0.1). Placebo injections will be given in different dosing regimens (according to the corresponding active treatment group) for the purpose of maintaining the blind. However, all placebo subjects across dosing regimens will be combined in 1 group for this analysis, since no difference in RR is expected if placebo is administered in different dosing regimens.

In Part 2, GSK3389404 treatment efficacy will be declared if the posterior probability that the difference in the RRs between that active group and the placebo is positive and is high (at least 90%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥90%, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

The primary efficacy analysis of Part 2 will be performed after all ongoing subjects in Part 2 complete the Day 85 visit (may or may not include the Japanese subjects from the optional Part 2 sub-study). At that time the database will be unblinded. Other primary analyses as mentioned above will also be performed. Details will be included in the RAP.

9.4.2. Secondary Analyses

Pharmacodynamics

Pharmacodynamic data (HBsAg, HBeAg, and HBV DNA) will be listed by subject and summarized descriptively by treatment group/HBeAg status in tabular and graphical formats, as appropriate.

Correlations between PD data in HBeAg-positive and HBeAg-negative subjects will be explored graphically. Correlation between PK parameters and PD parameters will also be explored graphically.

Pharmacokinetics

ISIS 505358 plasma concentration-time data will be listed by subject and summarized descriptively by treatment group and HBeAg status in tabular and graphical formats. ISIS 505358 PK parameters will be derived from the concentration-time profiles using WinNonlin. The derived PK parameters, including but not limited to $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, and $t_{½}$ will be listed by subject and summarized by treatment group and HBeAg status. Summaries may also combine treatment groups as applicable.

9.4.3. Other Analyses

Subject disposition, demographics, medical history, prior and concomitant medications, and study treatment exposure will be listed by subject and summarized descriptively for each part of the study separately.

Response will also be measured based on change from baseline in HBeAg level in HBeAg-positive subjects. Change from baseline will be summarized by treatment group and listed by subject and treatment group for each part of the study separately.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.4. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK/designee monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK/designee will monitor the study and site activity to verify the following:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor or designee will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK SOPs.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the

investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, or electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK/designee will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK/designee of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

10.8.1. Dose Escalation Committee

The decision to proceed to the next dose level of GSK3389404 in each cohort and to initiate Part 2 of the study will be made by a Dose Escalation Committee consisting of the principal investigator (or appropriate designee), medical monitor, GSK study team leader, GSK pharmacokineticist, a GSK GCSP representative, and GSK data manager, programmer, and statistician (appropriate designees may attend). The GSK study team will remain unblinded at an aggregate level throughout Part 1 of the study as detailed in Section 6.5.

Dosing decisions for each subsequent dosing cohort will be based on safety, tolerability, PK, and PD data from the previous dose levels investigated. Dose escalation decisions will be based on data through Day 3 obtained from at least 3 subjects receiving GSK3389404 at the prior dose level. The review data set will include listings for AEs, flagged vital signs, ECGs, laboratory findings (including liver function tests), and PK results derived from 24-hour plasma profiles, together with any available PD data. A maximum $AUC_{(0-\infty)}$ of 492.7 μg•h/mL or C_{max} of 52.7 μg/mL of GSK3389404 is not expected to be exceeded in any cohort.

10.8.2. Part 2 Safety Review

In Part 2, safety data from a sentinel group (1 subject from each treatment group and the corresponding matching placebo) will be reviewed by the GSK internal clinical team or SRT in a blinded manner. The remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure (but may include more data) in the sentinel group are reviewed. Safety data from all subjects will be reviewed by the GSK internal clinical team or SRT in a blinded manner on a regular basis thereafter.

The review data set will include listings for AEs, ISRs, flagged vital signs, ECGs, and laboratory findings (including liver function tests). All efforts will be made to maintain the study integrity and validity of study data.

10.8.2.1. Safety Review Team

The SRT is an internal GSK cross-functional team reviewing all available blinded safety data related to the project in an ongoing manner. The SRT is an internal GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety.

The SRT reviews will commence in Part 2 of the study, as the Dose Escalation Committee meetings will fulfil this purpose in Part 1.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACR	albumin to creatinine ratio
AE	adverse event
ALK	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRI	aspartate aminotransferase-platelet index
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0-24)}$	area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose
$AUC_{(0-\infty)}$	area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BLRM	Bayesian logistic regression model
BMI	body mass index
BMD	bone mineral density
BUN	blood urea nitrogen
CHB	chronic hepatitis B
CL/F	apparent subcutaneous plasma clearance
CKD-EPI	Chronic Kidney Disease Epidemiologic Collaboration
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DAIDS	Division of Acquired Immune Deficiency Syndrome
dL	deciliters
DMPK	drug metabolism and pharmacokinetics
DNA	deoxyribonucleic acid
EC_{90}	concentration that produces 90% of maximal effect
EC_{99}	concentration that produces 99% of maximal effect
ECG	electrocardiogram
EPIP	Electronic Protocol Inquiry Platform
ET	early termination
FSH	follicle stimulating hormone
GalNAc	N-acetyl galactosamine
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance

GFR	glomerular filtration rate
GSK	GlaxoSmithKline
H	hours
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B virus e-antigen
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HPF	high-power field
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDO	indoleamine 2,3 dioxygenase
IEC	Independent Ethics Committee
INR	international normalized ratio
ISR	injection site reaction
ITT	Intent-to-Treat
IU	international units
Kg	kilograms
kPa	kilopascals
L	liters
Lb	pounds
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
m^2	square meters
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
Mg	milligrams
Min	minutes
mL	milliliters
mm^3	cubic millimeters
MOE	methoxyethyl
Msec	milliseconds
MSDS	Material Safety Data Sheet
NCA	non-compartmental analysis
Ng	nanograms
NOAEL	no observed adverse effect level
Nucleos(t)ide	nucleoside or nucleotide
OAT	organic anion transporter
OCT	organic cation transporter

PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics(s)
PEG	pegylated
PK	pharmacokinetic(s)
PT	prothrombin time
QTcF	Fridericia's QT correction formula
RAP	Reporting and Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
RR	response rate
RR_{ACT}	response rate in the active group
RR_{PBO}	Response rate in the placebo group
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
SOP	standard operating procedure
SPEP	serum protein electrophoresis
SRM	Study Reference Manual
SRT	Safety Review Team
$t_{½}$	terminal half-life
TCM	traditional Chinese medicine
t_{max}	time of maximum observed concentration
U	units
UA	urinalysis
μg	micrograms
ULN	upper limit of normal
UPEP	urine protein electrophoresis
μmol	micromole
WBC	white blood cell

Trademark Information

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MedDRA
SAS
WinNonlin

12.2. Appendix 2: Liver Safety Required Actions and Follow-up Assessments

The procedures listed below are to be followed if a subject meets any of the liver chemistry stopping criteria defined in Section 5.4.1.

- Immediately withdraw the subject from study treatment.
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the Liver Event case report form (CRF).
- Complete the "Safety Follow-up Procedures" listed below.
- Upon completion of the safety follow-up, withdraw the subject from the study unless further safety follow-up is required.
- Do **not** re-challenge with study treatment

Safety Follow-up Procedures For Subjects 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.
- 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 subject's best approximation. Instructions for sample handling and shipping are included in the Study Reference Manual (SRM).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 1.5 X upper limit of normal (ULN)
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the Adverse Event (AE) CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are **required for subjects who meet the ALT and bilirubin stopping criteria** (Table 5) 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 subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) or Liver biopsy to evaluate liver disease.
    - The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. • 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 treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where 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.

12.3.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

i. Results in death

Is life-threatening

NOTE:

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

Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.3.4. Recording of AEs and SAEs

AEs 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) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

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

The DAIDS Table [DAIDS, 2014] 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.

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life Threatening
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions Grading Table

Cardiovascular:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities1 ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to <160 mmHg systolic OR 90 to <100 mmHg	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization
<18 years of age	>120/80 mmHg	≥95th to <99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 9th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	Not applicable	Not applicable	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Haemorrhage (with significant acute blood loss)	Not applicable	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *>16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
≤ *16 years of age*	1st degree AV block (PR interval >normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval2	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	Not applicable	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C
2. As per Bazett's formula

Dermatologic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Not applicable	Not applicable
Bruising	Localized to one area	Localized to more than one area	Generalized	Not applicable
Cellulitis	Not applicable	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	Not applicable	Not applicable
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	Not applicable	Not applicable
Petechiae	Localized to one area	Localized to more than one area	Generalized	Not applicable

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritus1 (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	Not applicable
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

1. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Endocrine and Metabolic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma, end organ failure)
Gynaecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	Not applicable
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipoatrophy1	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	Not applicable
Lipohypertrophy2	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	Not applicable

1. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
2. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Not applicable
Cholecystitis	Not applicable	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	Not applicable	Persistent constipation requiring regular use of dietary modifications, laxatives, or	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diarrhoea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis **Report only one and specify location**	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	Not applicable	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis)
Perforation (colon or rectum)	Not applicable	Not applicable	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	Not applicable	Not applicable
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	Not applicable	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia1 ≥ *30 years of age*	BMD t-score -2.5 to -1	Not applicable	Not applicable	Not applicable
<*30 years of age*	BMD z-score -2 to -1	Not applicable	Not applicable	Not applicable

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Osteoporosis[1] ≥ *30 years of age*	Not applicable	BMD t-score <-2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<30 years of age	**Not applicable**	**BMD z-score <-2**	**Pathologic fracture (e.g., compression fracture causing loss of vertebral height)**	**Pathologic fracture causing life-threatening consequences**

1. **Bone mineral density (BMD**) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Center for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	Not applicable	Not applicable	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioural, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part- time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay *<18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures **New Onset Seizure** ≥ 18 years of age	Not applicable	Not applicable	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
<18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting <5 minutes with <24 hours postictal state	Seizure lasting 5 to <20 minutes with <24 hours postictal state	Seizure lasting ≥20 minutes OR >24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	Not applicable	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	Not applicable

Pregnancy, Puerperium and Perinatal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Foetal Death or Stillbirth (report using mother's participant ID)	Not applicable	Not applicable	Foetal loss occurring at ≥20 weeks gestation	Not applicable
Preterm Delivery1 (report using mother's participant ID)	Delivery at 34 to <37 weeks gestational age	Delivery at 28 to <34 weeks gestational age	Delivery at 24 to <28 weeks gestational age	Delivery at <24 weeks gestational age
Spontaneous Abortion or Miscarriage2 (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	Not applicable

1. Definition: A delivery of a live-born neonate occurring at ≥ 20 to <37 weeks gestational age.
2. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.

Psychiatric:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	Not applicable
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social &	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social &	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnoea or Respiratory Distress *Report only one*	Dyspnoea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnoea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%	Dyspnoea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	Not applicable	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
<12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech- language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	Not applicable

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal oedema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Not applicable
Cytokine Release Syndrome1	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pain2 (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness3	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight4 >5 to 19 years of age	Not applicable	WHO BMI z-score <-2 to ≤ -3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
2 to 5 years of age	Not applicable	WHO Weight-for- height z-score <-2 to ≤ -3	WHO Weight-for- height z-score <-3	WHO Weight-for-height z-score <-3 with life- threatening consequences
<2 years of age	Not applicable	WHO Weight-for- length z-score <-2 to ≤-3	WHO Weight-for- length z-score <-3	WHO Weight-for-length z-score <-3 with life- threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Weight Loss (excludes postpartum weight loss)	Not applicable	5 to <9% loss in body weight from baseline	≥ 9 to <20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

1. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
2. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
3. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnoea
4. WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age

Urinary:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	Not applicable	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness1 *Report only one* *>15 years of age*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform	Potentially life- threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life- threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Induration or Swelling *Report only one* *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness, ≤** *15 years of age*	Same as for **Injection Site Erythema or Redness, ≤** *15 years of age*	Same as for **Injection Site Erythema or Redness, ≤** *15 years of age*	Same as for **Injection Site Erythema or Redness, ≤** *15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	Not applicable

1. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values – Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	Not applicable	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life- threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	Not applicable

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Alkalosis	Not applicable	pH >ULN to ≤ 7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life- threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin *Direct Bilirubin1, High* *>28 days of age*	Not applicable	Not applicable	>ULN	>ULN with life- threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to≤1 mg/dL	>1 to ≤1.5 mg/dL	>1.5 to ≤2 mg/dL	>2 mg/dL
Total Bilirubin, High *>28 days of age*	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ *28 days of age*	See Appendix 3 (Section 12.3.5.1.1). Total Bilirubin for Term and Preterm Neonates	See Appendix 3 (Section 12.3.5.1.1). Total Bilirubin for Term and Preterm Neonates	See Appendix 3 (Section 12.3.5.1.1). Total Bilirubin for Term and Preterm Neonates	See Appendix 3 (Section 12.3.5.1.1). Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) ≥ *7 days of age*	10.6 to <11.5 *2.65* to <*2.88*	11.5 to <12.5 *2.88* to <*3.13*	12.5 to <13.5 *3.13* to <*3.38*	≥13.5 ≥*3.38*
<*7 days of age*	11.5 to <12.4 *2.88* to <*3.10*	12.4 to <12.9 *3.10* to <*3.23*	12.9 to <13.5 *3.23* to <*3.38*	≥13.5 ≥*3.38*
Calcium (Ionized), High (mg/dL*; mmol/L*)	>ULN to <6.0 >*ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 ≥*.8*
Calcium, Low (mg/dL; *mmol/L*) ≥ *7 days of age*	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 <*1.53*
<*7 days of age*	6.5 to <7.5 *1.63 to <1.88*	6.0 to <6.5 *1.50 to <1.63*	5.50 to <6.0 *1.38 to <1.50*	<5.50 <*1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 <*LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 <*0.8*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac Troponin I, High	Not applicable	Not applicable	Not applicable	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5 x ULN OR Increase of 1.5 to <2.0 x above baseline	≥3.5 x ULN OR Increase of ≥2.0 x above baseline
Creatinine Clearance2 or eGFR, Low *Report only one*	Not applicable	<90 to 60 ml/min or ml/min/1.73 m2 OR 10 to <30% decrease from baseline	<60 to 30 ml/min or ml/min/1.73 m2 OR ≥30 to <50% decrease from baseline	<30 ml/min or ml/min/1.73 m2 OR ≥50% decrease from baseline or dialysis needed
Glucose *(mg/dL; mmol/L)* *Fasting, High*	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, Low (mg/dL; *mmol/L*) ≥ *1 month of age*	55 to 64 *3.05 to 3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
<1 month of age	50 to 54 *2.78 to 3.00*	40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH<7.3 without life-threatening consequences	Increased lactate with pH<7.3 with life- threatening consequences
Lipase, High	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) *Cholesterol, Fasting, High* ≥ *18 years of age*	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	Not applicable
<18 years of age	170 to <200 *4.40 to <5.15*	200 to <300 *5.15 to <7.77*	≥300 *≥7.77*	Not applicable
LDL, Fasting, High ≥ *18 years of age*	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	Not applicable

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
>2 to <18 years of age	110 to <130 *2.85 to <3.34*	130 to <190 *3.34 to <4.90*	≥190 *≥4.90*	Not applicable
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium3, Low (mEq/L; *mmol/L)*	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL*; mmol/L*) *>14 years of age*	2.0 to <LLN *0.81 to <LLN*	1.4 to <2.0 *0.65 to <0.81*	1.0 to <1.4 *0.32 to <0.65*	<1.0 *<0.32*
1 to 14 years of age	3.0 to <3.5 *0.97 to <1.13*	2.5 to <3.0 *0.81 to <0.97*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
<1 year of age	3.5 to <4.5 *1.13 to <1.45*	2.5 to <3.5 *0.81 to <1.13*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <135*	121 to <125 *121 to <125*	≤ 120 *≤ 120*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

1. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as grade 2, if <10% of the total bilirubin
2. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2)
3. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114

Hematology:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *>5 years of age* *(not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *>5 years of age* *(not HIV infected)*	600 to <650 *0.600 x 10^9 to <0.650 x 10^9*	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.350 x 10^9 to <0.500x10^9*	<350 *<0.350x10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	<400 *<0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	<750 *<0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x $10^9$to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	<1,500 *<1.500 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR *0.75 to <1.00 x LLN*	75 to <100 *0.75 to <1.00* OR *≥ 0.50 to <0.75 x LLN*	50 to <75 *0.50 to <0.75* OR *0.25 to <0.50 x LLN*	<50 *<0.50* OR <0.25 x LLN *OR Associated with gross bleeding*
Haemoglobin1**, Low** (g/dL; *mmol/L*)2				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
57 days of age to <13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INR, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to <3.0 x ULN	≥ 3.0 x ULN
Methaemoglobin (% haemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66 x ULN	1.66 to <2.33 x ULN	2.33 to <3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <124,999 *100.000 x 10^9 to <124.999 x 10^9*	50,000 to <100,000 *50.000 x 10^9 to <100.000 x 10^9*	25,000 to <50,000 *25.000 x 10^9 to <50.000 x 10^9*	<25,000 *<25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to <1.25 x ULN	1.25 to <1.50 x ULN	1.50 to <3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3*; cells/L*)				
>7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	<1,000 *<1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	<2,500 *<2.500 x 10^9*

1. Male and female sex is defined as sex at birth.
2. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading haemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Urinalysis:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	Not applicable
Haematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	Not applicable

12.3.5.1.1. Total Bilirubin Table for Term and Preterm Neonates:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin1**, High** (mg/dL; *µmol/L*)2 ***Term Neonate***3 *<24 hours of age*	4 to <7 *68.4 to <119.7*	7 to <10 *119.7 to <171*	10 to <17 *171 to <290.7*	≥17 *≥ 290.7*
24 to <48 hours of age	5 to <8 *85.5 to <136.8*	8 to <12 *136.8 to <205.2*	12 to <19 *205.2 to <324.9*	≥19 *≥324.9*
48 to <72 hours of age	8.5 to <13 *145.35 to <222.3*	13 to <15 *222.3 to <256.5*	15 to <22 *256.5 to <376.2*	≥22 *≥376.2*
72 hours to <7 days of age	11 to <16 *188.1 to <273.6*	16 to <18 *273.6 to <307.8*	18 to <24 *307.8 to <410.4*	≥24 *≥410.4*
7 to 28 days of age *(breast feeding)*	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age *(not breast feeding)*	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN
Preterm Neonate[20] *35 to <37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to <35 weeks gestational age and <7 days of age	Not applicable	Not applicable	10 to <14 *171 to <239.4*	≥14 *≥239.4*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
28 to <32 weeks gestational age and <7 days of age	Not applicable	Not applicable	6 to <10 *102.6 to <171*	≥10 *≥171*
<28 weeks gestational age and <7 days of age	Not applicable	Not applicable	5 to <8 *85.5 to <136.8*	≥8 *≥136.8*
7 to 28 days of age (breast feeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN

1. Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
2. A laboratory value of 1 mg/dL is equivalent to 17.1 μmol/L.
3. Definitions: Term is defined as ≥37 weeks gestational age; near-term, as ≥35 weeks gestational age; preterm, as <35weeks gestational age; and neonate, as 0 to 28 days of age.

12.3.5.2. Causality

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

12.3.5.3. Toxicity Management

ANEMIA

Grade 1 (mild) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 1 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, subjects may continue study treatment. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as

specified above, subjects will permanently discontinue study treatment and be withdrawn from the trial. Subjects should be followed up until resolution of anemia.

Grade 2 (moderate) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 2 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased > 50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, subjects may continue study treatment. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, subjects will permanently discontinue study treatment and be withdrawn from the trial. Consultation with a Hematologist should be considered. Subjects should be followed up until resolution of anemia.

Grade 3 (severe) or Grade 4 (potentially life threatening) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 3 or 4 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin
3. haptoglobin
4. reticulocyte count

Subjects will permanently discontinue study treatment and be withdrawn from the trial. Consultation with a Hematologist should be considered. Subjects should be followed up until resolution of anemia.

TOTAL BILIRUBIN ELEVATION

Grade 1 (mild) bilirubin elevation (1.1 - 1.5 times ULN) or Grade 2 (moderate) bilirubin elevation (1.6-2.5 times ULN):

Any bilirubin value above the ULN must be repeated and fractionated (direct and indirect bilirubin). Subjects may continue study treatment. Subjects should be followed up until resolution (return to baseline) of elevation.

Grade 3 (severe: 2.6-5.0 times ULN) or 4 (life-threatening: > 5.0 times ULN) bilirubin elevation:

Any bilirubin value above the ULN must be repeated and fractionated (direct and indirect bilirubin). Subjects will permanently discontinue study treatment and be withdrawn from

the trial. Subjects should be followed up until resolution (return to baseline) of bilirubin elevation.

AST AND ALT ELEVATION

See Appendix 2 (Section 12.2).

RASH

Grade 1 rash (Localized macular rash):

Subjects with Grade 1 rash should be evaluated by the Investigator immediately. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study treatment should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 rash may continue the study treatment at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study treatment, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

Grade 2 rash (Diffuse macular, maculopapular, or morbilliform rash OR Target lesions):

Subjects with Grade 2 rash should be evaluated by the Investigator immediately. Digital photographs should be obtained. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study treatment should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 rash may continue the study treatment at the discretion of the Investigator. It should be noted that oral mucosal **erosions** may be part of a Grade 2 rash. Any mucosal **ulceration** increases the severity of the rash to at least Grade 3. The subject should be advised to contact the

Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study treatment, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

Grade 3 rash (Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site):

Subjects with a Grade 3 rash will permanently discontinue the study treatment. The subject should be evaluated in the physician's office immediately and should be seen in the physician's office or contacted by phone every 2 days until the rash resolves. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

Grade 4 rash (Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)):

Subjects with a Grade 4 rash will permanently discontinue the study treatment. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Sponsor and medical monitor should be notified of this SAE within 24 hours via phone or fax. The subject should be closely followed every day until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritus without rash):

Subjects with Grade 1 allergic reaction should be evaluated by the Investigator immediately. The study treatment should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 allergic reaction may continue the study treatment at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study treatment, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

Grade 2 allergic reaction (Localized urticaria):

Subjects with Grade 2 allergic reaction should be evaluated by the Investigator immediately. The study treatment should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 allergic reaction may continue the study treatment at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study treatment, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 5.4.

Grade 3 allergic reaction (Generalized urticaria or angioedema):

Subjects will permanently discontinue the study treatment and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the AE and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):

Subjects will permanently discontinue the study treatment and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the AE and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definitions	Investigator Action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue Therapy
Grade 4	Anaphylaxis	Discontinue Therapy

12.3.5.4. Follow-up

Follow-up of AEs and SAEs

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

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to PPD/GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the ‘reviewed’ box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data

SAE reporting to GSK via electronic data collection tool
• If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to PPD Safety Hotline by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential and Collection of Pregnancy Information

12.4.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable) and for female subjects of reproductive potential (FRP).

Male subjects with female partners of child bearing potential and female subjects of child bearing potential must comply with the following contraception requirements from either the time of first dose of study treatment (male) or from at least 28 days prior to the first dose of study treatment (FRP) until Follow-up visit Day 169.

This list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Male vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's review of the male subject's (or female subject's male partner prior to the female subject's entry into the study) medical records, medical examination and/or semen analysis, or medical history interview. This documentation may be provided by male subjects, by female subjects on behalf of their partner, or by her partner.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
    - Injectable progestogen [Hatcher, 2011]
    - Contraceptive vaginal ring [Hatcher, 2011]
    - Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.4.2. Collection of Pregnancy Information

For female subjects that becomes pregnant during the study:

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion 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 treatment 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 subject who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study.

For female partners of a male study subject:

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study treatment.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.5. Appendix 5: Country Specific Requirements

If Japan conducts the optional Japanese Part 2 sub-study, Japan-specific requirements will be specified in a country-specific amendment or supplement protocol.

South Korea will exclude females of reproductive potential in Part 1 only as shown in the country-specific protocol amendment 4.

Otherwise, no country-specific requirements exist.

12.6. Appendix 6: Statistical Considerations for Part 2

12.6.1. Introduction

This document describes the Bayesian model based design for Part 2 of Study 205670 of GSK3389404 in chronic hepatitis B (CHB) subjects. The purpose of this section is to provide an overview of the trial design and simulation results. Analyses will be performed using Proc Markov Chain Monte Carlo (MCMC) procedure of SAS 9.3.

The primary efficacy objective of Part 2 of this study is to select an efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint, response rate (RR), based on reduction of hepatitis B surface antigen (HBsAg) level from baseline. A subject will be considered a responder if there is at least a 1.5 times log 10 IU/mL reduction of HBsAg levels from baseline anytime during the study. A model based probability inference approach in Bayesian framework will be used for decision-making.

In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. There are approximately 11 subjects in each of the active treatment groups and approximately 6 subjects in placebo. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and regimen.

12.6.2. Statistical Modeling

The RR data will be analyzed using a dose-response model. The posterior mean for each active treatment group will be derived from the posterior distribution of the response rates using a 3-parameter logistic regression model using weakly-informative priors for model parameters. Estimates for this model's parameters will be derived using the data generated within each treatment arm, i.e., this model will borrow degrees of freedom across active dose levels and regimens therefore providing higher power compared to pair-wise comparison given the small sample size of each treatment arm and low expected response rate for placebo.

A Bayesian logistic regression model (BLRM) [Neuenschwander, 2008] is considered to find an efficacious dose in this study.

For dose **d** and regimen **R**, the number of subjects with a response ($\mathbf{Y_{dr}}$) in a treatment arm of size $\mathbf{n_{dr}}$ is binomial. Therefore, $\mathbf{Y_{dr}}| \mathbf{n_{dr}} \sim$ Binomial ($\boldsymbol{\pi_{dr}}$, $\mathbf{n_{dr}}$), with RRs

$$\text{logit}(\pi_{dr}) = \alpha + \beta \log(d/d^*) + \gamma R,$$

where d is the active dose; R is the regimen (R=1 for regimen 1 and R=0 for regimen 2); d* is a reference dose allowing for the interpretation of α as the odds of a response at d*; β is the change in the log-odds of a response by a unit increase in log-dose; γ is the change in the log-odds of a response due to change in regimen. Since this is the first-in-patient, a weakly informative priors of the model parameters ($\alpha \sim$ N(0, var=100),

$\beta \sim N(0, var=25)$, $\gamma \sim N(0, var=9)$) are assumed. To justify the prior selection, a set of 1000 observations were generated from each of the prior distribution. The estimate of each of the parameters centers close to 0.5, with range between (0, 1) and standard deviation approximately 0.5. Posterior distribution of RRs of active treatment arms will be generated using BLRM.

Since it is not expected to have any responder in the placebo arm, posterior distribution of RRs is generated separately from a Beta distribution, i.e., Beta(0.1,0.1). Placebo injections will be given in different dosing regimens (according to the corresponding active treatment group) for the purpose of maintaining the blind. However, all placebo subjects across dosing regimens will be combined in 1 group for this analysis, since no difference in RR is expected if placebo is administered in different dosing regimens.

The difference between the posterior RRs between active treatment arm and placebo will be calculated to determine the probability of success (PoS) as described in Section 12.6.3.

12.6.3. Success Criteria

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 90%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥90%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

A large set of posterior mean of RRs for each treatment group will be generated by using MCMC samples from the posterior distribution using BLRM (for active) or beta distribution (placebo). Then the difference between posterior mean of each active treatment group and placebo (active – placebo) will be calculated for each of the MCMC sample. The number of times the difference greater than 0 over the parameter space (i.e. number of MCMC samples) provides the posterior probability of the difference in RRs between that active group and the placebo group is positive.

12.6.4. Scenarios for Testing

The treatments selected for Part 2 are 60 mg GSK3389404 weekly, 120 mg bi-weekly GSK3389404, 120 mg GSK3389404 weekly or placebo. . The description of treatment groups along with the sample size is provided in Table 17 A range of scenarios, as described in Table 18, were created to test the model performance.

Table 17 Treatment Description

Treatment Description	Treatment	Sample Size
Total monthly dose of 240 mg divided weekly (i.e., 60 mg once a week)	240W	11
Total monthly dose of 240 mg divided bi-weekly (i.e., 120 mg bi-weekly)	240BW	11
Total monthly dose of 480 mg divided weekly (i.e., 120 mg once a week)	480W	11
Matching placebo for each active treatment	PBO	6

A RR of 5% or below is considered for placebo or no treatment effect. A 30% or more absolute improvement in the RRs over placebo is considered an important treatment effect among subjects with CHB.

Table 18 Scenarios for Simulation

Scenario Number	Response Rate (%) (PBO, 240W, 240BW, 480W)	Description
1	(5, 5, 5, 5)	No treatment effect
2	(5, 30, 30, 30)	All of the active treatment groups are equally effective (medium effect size)
3	(5, 15, 15, 35)	Larger effect in higher dose group, bi-weekly dosing is equally effective as weekly
4	(5, 20, 15, 35)	Larger effect in higher dose group, weekly dosing has small effect

BW = bi-weekly; PBO = placebo; W = weekly

12.6.5. Simulations

Simulations are performed to calculate the operating characteristics of this model and to understand the model performance under each of the scenarios described in Table 18. Response data for 3 treatment groups are generated from binomial distributions using the sample size from Table 17 and response rates from Table 18. A set of 1000 datasets were simulated for each scenario. For each of the scenarios, average posterior means along with 90% credible intervals (CI), and average PoS are calculated over the sample space of 1000 simulations. Sensitivity of sample size is also provided using different cutoff points for PoS (e.g. 85%, 90%, 95% and 98%).

The above operating characteristics are also calculated for pair-wise comparison (i.e., without any model, based on difference in posterior distributions of individual treatment arm against placebo, both with Beta (0.1, 0.1) as prior distribution). In most of the scenarios, the decision of selecting an active treatment group is in agreement by both the methods. However, BLRM provided better operating characteristics (larger power and tighter CI). The probability of selecting an inefficacious treatment group is lower in BLRM compared to pair-wise method.

Simulation results for all scenarios are summarized in Table 19 to Table 22.

A cutoff point of 90% for PoS seems to provide reasonable probability for selecting an efficacious dose group given the sample size of this study.

Table 19 Simulation Results From Scenario 1

	Scenario 1		No Treatment Effect (PBO, 240W, 240BW, 480W): (5, 5, 5, 5)					
	Treatment	Posterior RR (%)	90% CI	Average PoS[1]	Power[2] Cutoff Points			
					85 %	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.71)					
	240W	6.05	(0.81,16.59)	53.17	30 .8	30.8	8.2	1.6
	240BM	5.72	(0.67,16.09)	53.05	31 .4	31.4	6.2	0.8
	480W	5.46	(0.63,15.53)	51.86	28 .7	28.7	6.6	0.6
BLRM	PBO	6.95	(0.71,21.34)					
	240W	4.88	(0.56,14.02)	57.83	21 .9	11.0	3.1	0.3
	240BW	5.3	(0.55,15.34)	58.67	31 .4	13.8	3.9	0.3
	480W	5.13	(0.52,15.04)	57.84	28 .7	13.7	4.7	0.2

Table 20 Simulation Results From Scenario 2

	Scenario 2		All of the active treatment groups are equally effective (medium effect size)					
			(PBO, 240W, 240BW, 480W): (5, 30, 30, 30)					
	Treatment	Posterior RR (%)	90% CI	Average PoS[1]	Power[2] Cutoff Points			
					85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)					
	240W	30.93	(12.67,53.01)	88.77	75.8	75.7	66.0	49.1
	240BM	30.09	(12.01,52.13)	88.26	75.9	75.8	65.7	49.1
	480W	30	(11.85,52.15)	88.6	75.8	75.8	66.2	49.2
BLRM	PBO	6.95	(0.71,21.34)					
	240W	30.38	(12.62,51.95)	89.53	76.2	74.1	64.9	46.7
	240BW	29.88	(12.05,51.71)	88.8	75.9	75.4	65.2	47.7
	480W	29.77	(11.84,51.77)	89.02	75.8	75.0	65.9	48.9

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected
2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Table 21 Simulation Results From Scenario 3

	Scenario 3		Larger effect in higher dose group, bi-weekly dosing is equally effective as weekly (PBO, 240W, 240BW, 480W): (5, 15, 15, 35)					
	Treatment	Posterior RR (%)	90% CI	Average PoS[1]	Power[2] Cutoff Points			
					85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)					
	240W	16.23	(4.27,34.07)	74.83	61.0	61.0	36.9	17.7
	240BM	15.58	(3.89,33.22)	74.26	60.3	60.2	37.7	15.5
	480W	34.86	(15.25,57.59)	91.23	80.5	80.4	70.9	58.3
BLRM	PBO	6.95	(0.71,21.34)					
	240W	16.27	(4.42,34.06)	79	61.0	56.7	35.2	15.1
	240BW	15.28	(3.81,32.93)	77.24	60.3	55.0	36.8	12.1
	480W	33.72	(14.57,56.2)	90.88	80.5	77.6	69.2	54.0

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected

2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Table 22 Simulation Results From Scenario 4

	Scenario 4		Larger effect in higher dose group, weekly dosing small effect (PBO, 240W, 240BW, 480W): (5, 20, 15, 35)					
	Treatment	Posterior RR (%)	90% CI	Average PoS[1]	Power[2] Cutoff Points			
					85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)					
	240W	20.9	(6.61,40.53)	80.33	65.9	65.9	48.5	27.8
	240BM	15.58	(3.89,33.2)	74.25	60.3	60.2	37.7	15.5
	480W	34.86	(15.24,57.6)	91.24	80.5	80.3	71.0	58.2
BLRM	PBO	6.95	(0.71,21.34)					
	240W	20.41	(6.57,39.67)	82.65	65.8	63.1	47.0	22.4
	240BW	15.61	(3.95,33.45)	77.78	60.3	56.7	37.0	12.7
	480W	34	(14.77,56.48)	91.03	80.5	77.8	69.2	55.0

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected

2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points (85,90,95,98%) over the sample space (i.e., 1000 simulations)

12.7. Appendix 7: Protocol Changes

12.7.1. Protocol changes for Amendment 01 (21-FEB-2017) from Original Protocol (21-Jun-2016)

Protocol Amendment 1 replaces the original protocol dated 21 Jun 2016 and applies to all study sites.

Protocol Amendment 1 is being implemented for the following reasons:

- To update the subject population in Part 2 from treatment naïve to treatment experienced.
    - Rationale: Investigator feedback is that the major focus should be on patients currently taking nucleos(t)ide, unless there is a scientific reason why GSK3389404 cannot be given with nucleos(t)ides. There is low potential for a drug-drug interaction with the nucleos(t)ides. Changing the population also eliminates the concern, albeit minor, that treatment-naïve subjects would remain untreated during the study.
- To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.
    - Rationale: This change provides the flexibility to explore a wider range of possible total monthly doses in Part 2. A maximum total monthly dose of 480 mg is supported by the preclinical package. The increase is also supported by the initial safety/tolerability and PK data from the first-in-human Study 202007, in which healthy volunteers were administered up to 480 mg for 4 weeks. Review of the initial safety and tolerability data shows a favorable benefit-risk profile.
- To reduce complexity and visit burden for subjects.
    - Rationale: Feedback from investigators suggests that the visit schedule in Part 1, particularly the overnight stay(s) will be too burdensome for subjects. The original protocol allowed for sites to admit subjects on Day -1 to complete Day 1 assessments, and also required subjects to stay overnight between Day 1 and Day 2 of the study. The amendment makes overnight stays optional, and eliminates the Day 2 assessments. Day 3 assessments will remain. Based on the results of the first-in-human Study 202007, removal of the Day 2 assessments should not impact subject safety.
- To make minor edits for clarity and typographical errors (these minor edits are not included in the list of changes).

LIST OF CHANGES

Title Page, Author (s)

Rationale for change: new clinical team member added.

Original Text

PPD

Amended Text

PPD

Section 1, Rationale, Paragraph 1, Last Sentence

Rationale for change: to update the subject population in Part 2 from treatment naïve to treatment experienced.

Original Text:

Data from this study will support subsequent studies by providing an early assessment of safety and PD in the target patient population when GSK3389404 is administered as monotherapy.

Amended Text:

Data from this study will support subsequent studies by providing an early assessment of safety and PD in the target patient population when GSK3389404 is administered as monotherapy **(Part 1) or adjunctive therapy (Part 2)**.

Section 1, Objective(s)/Endpoints(s), Exploratory, (New objective added)

Rationale for change: addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B.

Original Text:

Not applicable.

Amended Text:

To describe the seroconversion of subjects, defined as presence of HBV surface antibody (HBsAb) (Part 2 only)	**Rate of seroconversion.**

Section 1, Overall Design, Paragraph 4, Sentence 3

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

The dose levels and regimens for Part 2 will be selected after review of safety (at a minimum of adverse events [AEs], laboratory chemistry, hematology, and electrocardiogram [ECG]), PK, and PD (HBsAg levels and HBV DNA) data from Part 1 (through Day 3) but will not exceed a total monthly SC dose of 240 mg.

Amended Text:

The dose levels and regimens for Part 2 will be selected after review of safety (at a minimum of adverse events [AEs], laboratory chemistry, hematology, and electrocardiogram [ECG]), PK, and PD (HBsAg levels and HBV DNA) data from Part 1 (through Day 3) but will not exceed a total monthly SC dose of ~~240~~**480** mg.

Section 1, Overall Design, Paragraph 4, (New sentence 5)

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

Not applicable.

Amended Text:

However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen.

Section 1, Treatment Arms and Duration, Paragraph 1, Bullet 2 (and sub-bullets) and Bullet 3

Rationale for change: to reduce complexity and visit burden for subjects.

Original Text:

- A 2 to 4-day in-house period is planned.
  - At most, 4-day, 3-night in-house period is planned (Day -1 to Day 3). At a minimum, a 2-day, 1 night in-house period is required (Day 1 to Day 2).
    - Day -1 admission is optional based on laboratory capabilities and study site/subject preference.

- An in-house stay is required from Day 1 to Day 2.
- Day 3 is an outpatient visit, but subjects may stay in-house until Day 3 assessments are completed.

o Dosing will take place on Day 1. The SC dose will be administered per cohort assignment (Cohorts A, B, C, C1, or D) and randomized treatment assignment (GSK3389404 or placebo).

Amended Text:

- ~~A 2 to 4-day in-house period is planned.~~ **Dosing will take place on Day 1 with follow-up on Day 3.**
  - ~~At most, 4-day, 3-night in-house period is planned (Day -1 to Day 3). At a minimum, a 2-day, 1 night in-house period is required (Day 1 to Day 2).~~ **Based on subject and study site preference, subjects have the option to be domiciled at the study site or present to the study site as outpatients**.
    - ~~Day -1~~ **aAdmission to the study site** is optional ~~based on laboratory capabilities and study site/subject preference~~ **from Day -1 to Day 2**.
      - ~~An in-house stay is required from Day 1 to Day 2~~ **Subjects admitted to the study site may be discharged Day 1, Day 2, or Day 3, based on subject and study site preference**.
      - ~~Day 3 is an outpatient visit, but subjects may stay in-house until Day 3 assessments are completed~~ **Subjects may present as outpatients on Day 1 and/or Day 3, based on subject or study site preference.**
  - o ~~Dosing will take place~~ ~~o~~**On** Day 1**,**~~.~~ ~~T~~**the** SC dose will be administered per cohort assignment (Cohorts A, B, C, C1, or D) and randomized treatment assignment (GSK3389404 or placebo).

Section 1, Treatment Arms and Duration, Paragraph 2, Bullet 2 and new sub-bullet

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

- An expected study treatment exposure of up to 85 days is planned where subjects will receive multiple SC doses of GSK3389404 (≤240 mg total monthly dose) or placebo at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens.

Amended Text:

- An expected study treatment exposure of up to 85 days is planned where subjects will receive multiple SC doses of GSK3389404 (≤~~240~~**480** mg total monthly dose) or placebo at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens.

- **The total monthly SC dose of 480 mg will only be explored in a once weekly or bi weekly (every 2 weeks) dosing regimen.**

Section 1, Treatment Arms and Duration, Paragraph 2, Bullet 2, last sub-bullet, sub-sub bullets 1, 2, and 3

Rationale for change: To make minor edits for clarity

Original Text:

- For once weekly dosing, subjects will be administered as a SC dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.
- For bi-weekly (every 2 weeks) dosing, subjects will be administered as a SC dose on Days 1, 15, 29, 43, 57, and 71.
- For monthly dosing, subjects will be administered as a SC dose on Days 1, 29, and 57.

Amended Text:

- For once weekly dosing, subjects will be administered **GSK3389404 or placebo** as a SC dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.
- For bi-weekly (every 2 weeks) dosing, subjects will be administered **GSK3389404 or placebo** as a SC dose on Days 1, 15, 29, 43, 57, and 71.
- For monthly dosing, subjects will be administered **GSK3389404 or placebo** as a SC dose on Days 1, 29, and 57.

Section 1, Type and Number of Subjects, Paragraph 1, Sentence 1

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Adult male and female subjects with CHB between18 and 70 years of age, inclusive, and not currently receiving CHB treatment are planned for inclusion.

Amended Text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive, and not currently receiving CHB treatment **(Part 1) or currently on a stable nucleos(t)ide regimen (Part 2)** are planned for inclusion.

Section 2.1, Study Rationale, Paragraph 1, Last Sentence

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Data from this study will thus support subsequent studies by providing an early assessment of safety and PD in the target patient population when GSK3389404 is administered as monotherapy.

Amended Text:

Data from this study will thus support subsequent studies by providing an early assessment of safety and PD in the target patient population when GSK3389404 is administered as monotherapy **(Part 1) or adjunctive therapy (Part 2)**.

Section 3, Objectives and Endpoints, Exploratory, (New objective added)

Rationale for change: addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

Not applicable.

Amended Text:

To describe the seroconversion of subjects, defined as presence of HBV surface antibody (HBsAb) (Part 2 only)	**Rate of seroconversion.**

Section 4.1, Overall Study Design, Paragraph 4, Sentence 4

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

The dose levels and regimens for Part 2 will be selected after a review of Part 1 safety, (at a minimum of adverse events [AEs], laboratory chemistry and hematology and electrocardiogram [ECG]), PK, and PD data (HBsAg and HBV DNA) (through Day 3) but will not exceed a total monthly dose of 240 mg.

Amended Text:

The dose levels and regimens for Part 2 will be selected after a review of Part 1 safety, (at a minimum of adverse events [AEs], laboratory chemistry and hematology and electrocardiogram [ECG]), PK, and PD data (HBsAg and HBV DNA) (through Day 3) but will not exceed a total monthly dose of ~~240~~**480** mg.

Section 4.1, Overall Study Design, Paragraph 4, (New sentence 6)

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

Not applicable.

Amended Text:

However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen.

Section 4.1, Overall Study Design, Figure 2, Footnote 4

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

1. Total monthly dose may be divided into weekly, bi-weekly (every two weeks), and/or monthly dosing, and total monthly dose will not exceed 240 mg.

Amended Text:

4. Total monthly dose may be divided into weekly, bi-weekly (every ~~two~~ **2** weeks), and/or monthly dosing, and total monthly dose will not exceed ~~240~~**480** mg. **However, the total monthly SC dose of 480 mg will only be explored in a weekly or bi-weekly dosing regimen.**

Section 4.2, Treatment Arms and Duration, Paragraph 2, Bullet 1 and Sub-bullets, Bullet 2 and Sub-bullets, Bullet 3, Bullet 4 and Sub-bullets, and Paragraph 3

Rationale for change: to reduce complexity and visit burden for subjects.

Original Text:

For the treatment period, a 2 to 4-day in-house stay is planned.

- Day -1 admission is optional, based on laboratory capabilities and study site/subject preference.
  - The study site/subject may use Day -1 as an outpatient visit for assessments and blood sample collection.
  - If the subject is willing to arrive early and the site is capable (early admission available and critical laboratory result turn-around is available prior to randomization), subjects may be admitted on Day 1 with all Day -1 assessments conducted pre-dose.
- An in-house stay is required from Day 1 to Day 2.
  - Subjects will receive a SC dose of GSK3389404 or placebo on Day 1. Subjects will remain in the study site until completion of the protocol-specified procedures on Day 2.
- Day 3 is an outpatient visit, but subjects may stay in-house until Day 3 assessments are completed.
- All in-house period options are listed below
  - 4 day, 3 night stay: Day -1 admission, Day 3 discharge
  - 3 day, 2 night stay: Day -1 admission, Day 2 discharge
  - 3 day, 2 night stay: Day 1 admission, Day 3 discharge
  - 2 day, 1 night stay: Day 1 admission, Day 2 discharge

Amended Text:

~~For the treatment period, a 2 to 4-day in-house stay is planned~~ **Subjects will receive a SC dose of GSK3389404 or placebo on Day 1,** ~~and~~ **with post-treatment follow-up on Day 3**.

- ~~Day -1 admission is optional, based on laboratory capabilities and study site/subject preference~~ **Based on subject and study site preference, subjects have the option to be domiciled at the study site or present to the study site as outpatients**.
  - ~~The study site/subject may use Day -1 as an outpatient visit for assessments and blood sample collection~~ **Admission to the study site is optional from Day -1 to Day 2.**
  - ~~If the subject is willing to arrive early and the site is capable (early admission available and critical laboratory result turn-around is available prior to randomization), subjects may be admitted on Day 1 with all Day -1 assessments conducted pre-dose~~ **Subjects admitted to the study site may be discharged Day 1, Day 2, or Day 3, based on subject and study site preference**.

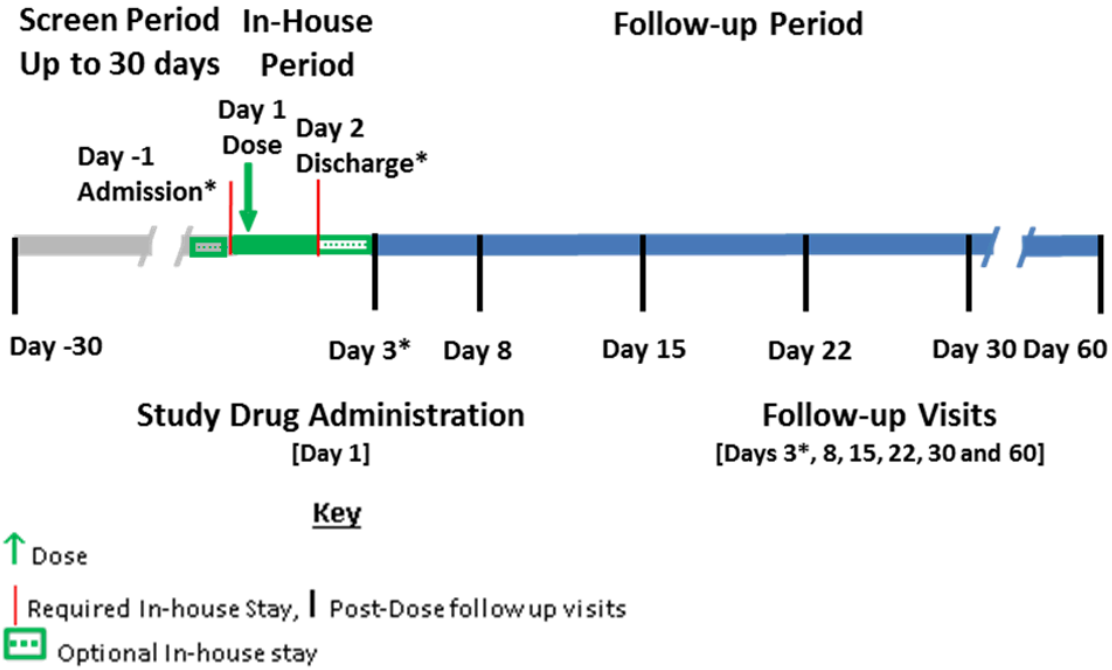
- **Subjects may present as outpatients on Day 1 and/or Day 3, based on subject or study site preference.**

- ~~An in-house stay is required from Day 1 to Day 2.~~
  - ~~Subjects will receive a SC dose of GSK3389404 or placebo on Day 1. Subjects will remain in the study site until completion of the protocol-specified procedures on Day 2.~~
- ~~Day 3 is an outpatient visit, but subjects may stay in-house until Day 3 assessments are completed.~~
- ~~All in-house period options are listed below~~
  - ~~4 day, 3 night stay: Day -1 admission, Day 3 discharge~~
  - ~~3 day, 2 night stay: Day -1 admission, Day 2 discharge~~
  - ~~3 day, 2 night stay: Day 1 admission, Day 3 discharge~~
  - ~~2 day, 1 night stay: Day 1 admission, Day 2 discharge~~

Section 4.2, Treatment Arms and Duration, Figure 3

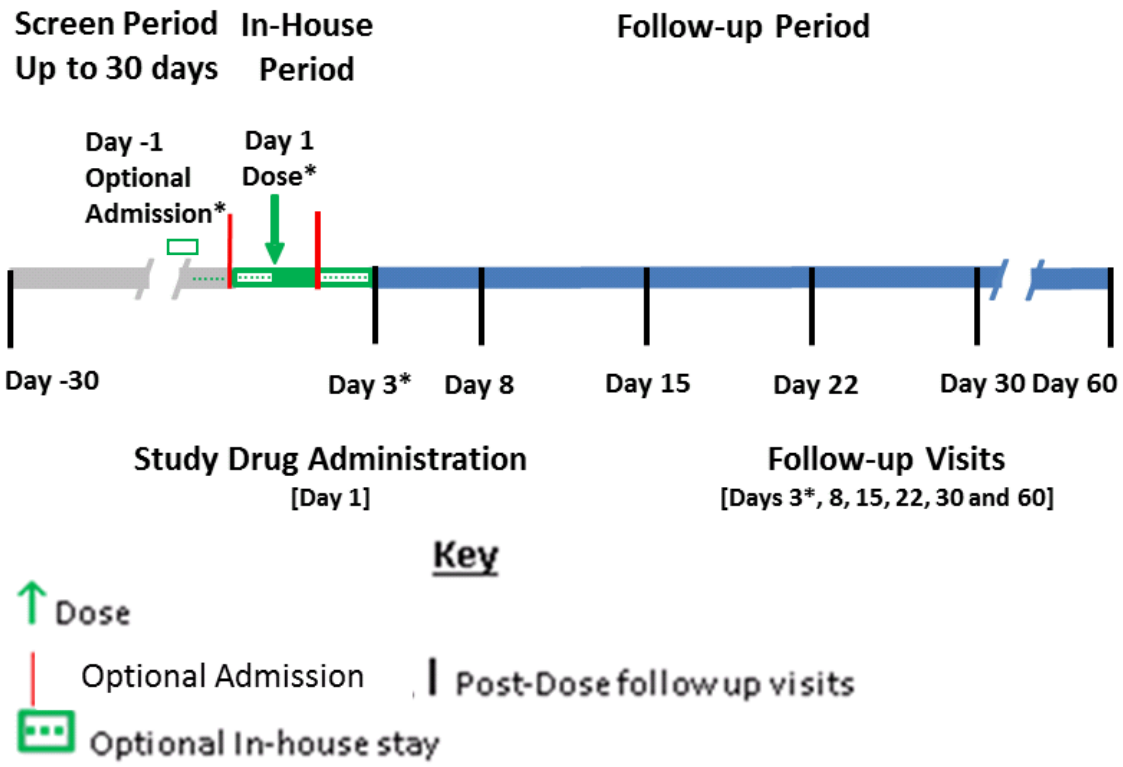
Rationale for change: to reduce complexity and visit burden for subjects.

Original Text:



Note: Five cohorts are planned to received a SC dose of GSK3389404 (30 mg to ≤240 mg) or placebo
* Day -1 admission is optional based on laboratory capabilities and study site/subject preference. In-house stay is required from Day 1 to Day 2. Day 3 is an outpatient visit, but subjects may remain in-house until all Day 3 assessments are completed.

Amended Text:



Note: Five cohorts are planned to received a SC dose of GSK3389404 (30 mg to ≤240 mg) or placebo

* ~~Day -1 admission is~~**In-house stays are** optional from Day -1 to Day 3 based on ~~laboratory capabilities and~~ study site/subject preference. ~~In-house stay is required from Day 1 to Day 2. Day 3 is an outpatient visit, but~~ **No study procedures are scheduled for Day 2 but** subjects may remain in-house until all Day 3 assessments are completed.

Section 4.2, Treatment Arms and Duration, Paragraph 4, Sentence 2 and new Sentence 3

Rationale for change: to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

Subjects will receive multiple SC doses of GSK3389404 (≤240 mg total monthly dose) or placebo (Figure 2) at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens.

Amended Text:

Subjects will receive multiple SC doses of GSK3389404 (≤~~240~~**480** mg total monthly dose) or placebo (Figure 2) at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens. **However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly dosing regimen.**

Section 4.3, Type and Number of Subjects, Paragraph 1, Sentence 1

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Adult male and female subjects with CHB between18 and 70 years of age, inclusive, and not currently receiving CHB treatment are planned for inclusion.

Amended Text

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive, and not currently receiving CHB treatment **(Part 1) or currently on a stable nucleos(t)ide regimen (Part 2)** are planned for inclusion.

Section 4.5.1, Observed Human Pharmacokinetics

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

GSK3389404 has been administered as single doses to healthy adult subjects at doses of 10 to 120 mg in Study 202007, a Phase I, first time in human, randomized, double-blind, placebo-controlled, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404. At the time of this protocol writing, the SAD part of Study 202007 has been completed, and the multiple ascending dose part is ongoing. The preliminary human PK parameters are presented in Table 1. Based on preliminary PK data, GSK3389404 showed dose-proportional PK with a meant $t_{½}$ of 4 to 5 hours at a dose range of 10 to 120 mg. The preliminary observed human PK data were evaluated using non-compartmental analysis (NCA) in Phoenix WinNonlin version 6.3.

Table 1 Summary of Selected Preliminary Plasma GSK3389404 Pharmacokinetic Parameters in Humans

Dose (mg)	N[1]	C_{max}[2] (ng/mL)	t_{max}[3] (h)	$t_{½}$[2] (h)	$AUC_{(0-\infty)}$[2] (h•ng/mL)
10	6	90 (24)	1 (1 - 4)	3.8 (66)	614 (27)
30	5	295 (69)	2 (1 - 2)	3.7 (81)	1968 (35)
60	6	512 (57)	3 (1 - 4)	5.1 (71)	4578 (30)
120	6	803 (49)	4 (3 - 4)	4.1 (29)	7718 (35)

1. At the 30-mg dose, the pharmacokinetic profile in 1 subject was atypical and not evaluable.
2. Data are presented as geometric mean (geometric coefficient of variation %)
3. Data are presented as Median (range)

Amended Text:

GSK3389404 has been administered ~~as single doses~~ to healthy adult subjects **in Study 202007 as single SC doses** at doses of 10 to 120 mg**. or as repeated SC doses (once weekly for 4 weeks) at doses of 30 to 120 mg. Study 202007 was** ~~in Study 202007~~, a Phase I, first time in human, randomized, double-blind, placebo-controlled, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404. At the time of this protocol writing, the SAD part of Study 202007 has been completed, and the multiple ascending dose part is ongoing. The preliminary human PK parameters are presented in Table 1. Based on preliminary PK data, GSK3389404 showed dose-proportional PK with a **mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose.** ~~meant $t_{½}$ of 4 to 5 hours at a dose range of 10 to 120 mg~~. The preliminary observed human PK data were evaluated using non-compartmental analysis (NCA) in Phoenix WinNonlin version 6.3. **All ISIS50538 (GSK3228836) plasma concentrations were non-quantifiable.**

Table 1 Summary of Selected Preliminary Plasma GSK3389404 Pharmacokinetic Parameters in Humans

~~Dose (mg)~~	~~N[1]~~	~~C_{max}[2] (ng/mL)~~	~~t_{max}[3] (h)~~	~~$t_{½}$[2] (h)~~	~~$AUC_{(0-\infty)}$[2] (h•ng/mL)~~
~~10~~	~~6~~	~~90 (24)~~	~~1 (1 - 4)~~	~~3.8 (66)~~	~~614 (27)~~
~~30~~	~~5~~	~~295 (69)~~	~~2 (1 - 2)~~	~~3.7 (81)~~	~~1968 (35)~~
~~60~~	~~6~~	~~512 (57)~~	~~3 (1 - 4)~~	~~5.1 (71)~~	~~4578 (30)~~
~~120~~	~~6~~	~~803 (49)~~	~~4 (3 - 4)~~	~~4.1 (29)~~	~~7718 (35)~~

~~1. At the 30 mg dose, the pharmacokinetic profile in 1 subject was atypical and not evaluable.~~
~~2. Data are presented as geometric mean (geometric coefficient of variation %)~~
~~3. Data are presented as Median (range)~~

Dose (mg)	**10**	**30**			**60**			**120**		
Cohort[1]	**A**	**B**	**E**	**E**	**C**	**F**	**F**	**D**	**G**	**G**
Day	**1**	**1**	**1**	**22**	**1**	**1**	**22**	**1**	**1**	**22**
N	**6**	**5[2]**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Half life[3] (hr)	**3.8 (66)**	**3.7 (81)**	**3.0 (34)**	**4.1 (61)**	**5.1 (71)**	**5.0 (206)**	**3.1 (51)**	**4.1 (29)**	**3.7 (43)**	**3.4 (38)**
T_{max}[4] (hr)	**1 (1-4)**	**2 (1-2)**	**2 (1-4)**	**2 (1-4)**	**3 (1-4)**	**2 (2-2)**	**2 (1.5-4)**	**4 (3-4)**	**2 (1.5-4)**	**2 (2-4)**
C_{max}[3] (ng/mL)	**90 (24)**	**295 (69)**	**228 (32)**	**194 (20)**	**512 (57)**	**692 (35)**	**577 (43)**	**803 (49)**	**1167 (50)**	**1107 (55)**
$AUC_{(0-\infty)}$[3] (ng*hr/mL)	**614 (27)**	**1969 (35)**	**1394 (24)**	**1526 (34)**	**4578 (30)**	**5875 (52)**	**3966 (23)**	**7718 (35)**	**8039 (36)**	**8640 (32)**
Fold coverage C_{max}[5]	**642**	**197**	**255**	**298**	**113**	**84**	**100**	**72**	**50**	**52**
Fold coverage	**759**	**237**	**334**	**305**	**102**	**79**	**117**	**60**	**58**	**54**

AUC[5]										

1. **Cohort A – D were single dose cohorts. Cohort E – G were multiple dose cohorts (weekly dose for 4 weeks).**
2. **In Cohort B (30-mg single) dose, the pharmacokinetic profile in one subject was atypical and not evaluable.**
3. **Data are presented as geometric mean (geometric coefficient of variation %).**
4. **Data are presented as Median (range).**
5. **Fold coverage based on monkey NOAEL (no observed adverse effect level): NOAEL Cmax = 57.9 μg/mL and NOAEL $AUC_{(0-\infty)}$ = 465.7 μg•h/mL at 30 mg/kg/week.**

Section 4.5.2, Safety Margin Calculations, Paragraph 2

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

Based on observed PK data in healthy adult subjects (Study 202007), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is 72-fold and 60-fold lower than the monkey NOAEL C_{max} and AUC, respectively (Table 1).

Amended Text:

Based on observed PK data in healthy adult subjects (Study 202007), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is ~~72-fold and 60-fold~~ **at least 50-fold** lower than the monkey NOAEL C_{max} and AUC, respectively (Table 1).

Section 4.5.2, Safety Margin Calculations, Table 2, Header Row

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

Human Dose (mg)	Observed GSK3389404 Cmax (ng/mL)1	Observed GSK3389404 AUC (h•ng/mL)1	Predicted Parent Liver Concentration (μg/g)2	Fold Coverage Cmax3	Fold Coverage AUC3	Fold coverage of estimated human liver concentration from Phase I Parent Study4

Amended Text:

Human Dose (mg)	Observed GSK3389404 Plasma Cmax (ng/mL)1	Observed GSK3389404 Plasma AUC (h•ng/mL)1	Predicted Parent Liver Concentration (μg/g)2	Fold Coverage Plasma Cmax3	Fold Coverage Plasma AUC3	Fold Coverage Of Estimated Human Liver Concentration from Phase I Parent Study4

Section 4.5.2, Safety Margin Calculations, Table 2, Last Row

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

240	1728[5]	15992[5]	59.0	34[5]	29[5]	8

Amended Text:

240	1728[5]	15992[5]	59.0	34[5]	29[5]	8

Section 4.5.2, Safety Margin Calculations, Table 2, Footnote 3

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg. Minor edits for clarity.

Original Text:

Fold coverage based on monkey NOAEL; GSK3389404 C_{max} = 57.9 µg/mL and $AUC_{(0-\infty)}$ = 465.7 µg•h/mL at 30 mg/kg/week.

Amended Text:

Fold coverage based on monkey NOAEL; GSK3389404 **plasma** C_{max} = 57.9 µg/mL and **plasma** $AUC_{(0-\infty)}$ = 465.7 µg•h/mL at 30 mg/kg/week.

Section 4.5.2, Safety Margin Calculations, Table 2, Footnote 5

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (10 to 120 mg) assuming dose proportionality.

Amended Text:

Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (10 to 120 mg) ~~assuming~~ **given** dose proportionality.

Section 4.5.3, In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, Paragraph 1

Rationale for change: To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

The maximum planned dose in the multiple dose cohorts (total monthly dose not exceeding 240 mg GSK3389404) was selected based on the in vivo exposure-response relationship of GSK3389404.

Amended Text:

The maximum planned dose in the multiple dose cohorts (total monthly dose not exceeding ~~240~~**480** mg GSK3389404) was selected based on the in vivo exposure-response relationship of GSK3389404.

Section 4.5.3, In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, Paragraph 5

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

Thus, in order to knockdown the target gene 90% or 99%, these data suggest that Study 205670 should explore SC doses of GSK3389404 predicted to yield human liver tissue concentrations of ISIS 505358 between EC_{90} (5.9 μg/g) and EC_{99} (33 μg/g). Based on observed liver tissue concentration in the monkey, it is estimated that a 60 mg weekly SC injection of GSK3389404 over 4 weeks would reach a human liver tissue concentration of 40.4 μg/g (>EC_{99}), assuming the liver tissue concentration between monkey and human is similar on a mg/kg basis (Table 3).

Amended Text:

Thus, in order to knockdown the target gene ~~90% or~~ 99%, these data suggest that Study 205670 should explore SC doses of GSK3389404 predicted to yield human liver tissue concentrations of ISIS 505358 **that will achieve** ~~between EC_{90} (5.9 μg/g) and~~ EC_{99} (33 μg/g). Based on observed liver tissue concentration in the monkey, it is estimated that a ~~60~~ **30** mg weekly SC injection of GSK3389404 ~~over 4 weeks~~ would reach a human liver tissue concentration of **41**~~40.4~~ μg/g (>EC_{99}) **after 13 weeks**, assuming the liver tissue concentration between monkey and human is similar on a mg/kg basis (Table 3). **However, greater clinical efficacy may be achieved if HBsAg is reduced by >99%. Thus, a total monthly dose not exceeding 480 mg GSK3389404 (weekly doses of 120 mg or bi-weekly doses of 240 mg) may be selected for Part 2.**

Section 4.5.3, In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, Table 3

Rationale for change: To provide supporting data to increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg.

Original Text:

Table 3 GSK3389404 Plasma C_{max} and AUC and Monkey NOAEL Exposure Fold Coverage Following Repeat Weekly SC Administration of GSK3389404 for 4 Weeks in Humans

Human Dose (mg)	Predicted GSK3389404 C_{max} (ng/mL)[1]	Predicted GSK3389404 AUC (h•ng/mL)[1]	Predicted Parent Liver Concentration (μg/g)[2]	Fold Coverage C_{max}[3]	Fold Coverage AUC[3]	Fold coverage of estimated human liver concentration from Phase I Parent Study[4]
30	295	1968	20.5	197	237	22.0
60	512	4578	40.4	113	102	11.1
120	803	7718	78.4	72	60	5.7
240	1728	15922	147.6	34	29	3.0

NOAEL = no observed adverse effect level

1. Predicted based on observed GSK3389404 human PK data at 10 to 120 mg in Study 202007.
2. Liver concentration in transgenic mice at 4 weeks after repeated once weekly doses was about 50% of that at 13 weeks (steady state) after repeated once weekly doses. Human steady state liver concentration of parent compound (ISIS 505358) was estimated based on 13-week monkey liver tissue concentration and assumed to be 50% of that at steady state. Liver concentration was fit to E_{max} model and then extrapolated.
3. Fold coverage based on monkey NOAEL; GSK3389404 C_{max} = 57.9 μg/mL and $AUC_{(0-\infty)}$ = 465.75 μg•h/mL at 30 mg/kg/week.
4. At 450 mg of ISIS 505358 (the highest dose in the ISIS 50538 first time in human study), human liver concentration (4 weeks) = 450 μg/g, based on allometric scaling [Geary, 2009]. Fold coverage = 450 μg/g divided by the predicted liver concentration.

Amended Text:

Table 3 GSK3389404 Plasma C_{max} and AUC and Monkey NOAEL Exposure Fold Coverage Following Repeat **Weekly or Bi-weekly (every 2 weeks)** SC Administration of GSK3389404 for **13** Weeks in Humans

~~Human Dose (mg)~~	~~Predicted GSK3389404 Cmax (ng/mL)[1]~~	~~Predicted GSK3389404 AUC (h•ng/mL)[1]~~	~~Predicted Parent Liver Concentration (μg/g)[2]~~	~~Fold Coverage Cmax[3]~~	~~Fold Coverage AUC[3]~~	~~Fold coverage of estimated human liver concentration from Phase I~~

						~~**Parent Study**[4]~~
~~30~~	~~295~~	~~1968~~	~~20.5~~	~~197~~	~~237~~	~~22.0~~
~~60~~	~~512~~	~~4578~~	~~40.4~~	~~113~~	~~102~~	~~11.1~~
~~120~~	~~803~~	~~7718~~	~~78.4~~	~~72~~	~~60~~	~~5.7~~
~~240~~	~~1728~~	~~15922~~	~~147.6~~	~~34~~	~~29~~	~~3.0~~

~~NOAEL = no observed adverse effect level~~

1. ~~Predicted based on observed GSK3389404 human PK data at 10 to 120 mg in Study 202007.~~
2. ~~Liver concentration in transgenic mice at 4 weeks after repeated once weekly doses was about 50% of that at 13 weeks (steady state) after repeated once weekly doses. Human steady state liver concentration of parent compound (ISIS 505358) was estimated based on 13-week monkey liver tissue concentration and assumed to be 50% of that at steady state. Liver concentration was fit to E_{max} model and then extrapolated.~~
3. ~~Fold coverage based on monkey NOAEL; GSK3389404 C_{max} = 57.9 μg/mL and $AUC_{(0-\infty)}$ = 465.75 μg•h/mL at 30 mg/kg/week.~~
4. ~~At 450 mg of ISIS 505358 (the highest dose in the ISIS 50538 first time in human study), human liver concentration (4 weeks) = 450 μg/g, based on allometric scaling [Geary, 2009]. Fold coverage = 450 μg/g divided by the predicted liver concentration.~~

Human Total Monthly Dose (mg)	**Human Repeat Dose (mg)[1]**	**Observed GSK3389404 Plasma C_{max} (ng/mL)[2]**	**Observed GSK3389404 Plasma AUC (h•ng/mL)[2]**	**Predicted Parent Liver Concentration At Week 13 (μg/g)[3]**	**Observed Fold Coverage Plasma C_{max}[4]**	**Observed Fold Coverage Plasma AUC[4]**	**Fold Coverage Of Predicted Human Liver Concentration at Week 13[5]**
120	**30 QW**	**194**	**1526**	**41**	**298**	**305**	**34**
240	**60 QW**	**577**	**3966**	**81**	**100**	**117**	**17**
480	**120 QW**	**1107**	**8640**	**157**	**52**	**54**	**9**
480	**240 Q2W**	**2200**	**16769**	**157**	**26**	**28**	**9**

NOAEL = no observed adverse effect level

1. **QW: dose every week. Q2W: dose every 2 weeks.**
2. **Geometric mean of GSK3389404 plasma human PK observed following repeat weekly SC dose of 30 to 120 mg for 4 weeks in Study 202007. The values for 240 mg were predicted**
3. **Human liver concentration of parent compound (ISIS 505358) at week 13 was estimated based on 13-week monkey liver tissue concentration (an average of 1404 μg/g at 30 mg/kg/week for 13 weeks). Liver concentration was fit to E_{max} model and then extrapolated.**
4. **Fold coverage based on monkey NOAEL (30 mg/kg/week for 13 weeks): GSK3389404 plasma C_{max} = 57.9 μg/mL and plasma $AUC_{(0-\infty)}$ = 465.75 μg•h/mL. Liver tissue concentration of parent compound (ISIS 505358) = 1404 μg/g.**
5. **Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (30 to 120 mg) given dose proportionality**

Section 4.5.4, Dose Escalation Justification, Paragraph 1, Sentence 4

Rationale for change: To make minor edits for clarity.

Original Text:

Escalation to the next higher single or to Part 2 will only proceed after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and the investigator at the Dose Escalation Committee meeting (Section 10.8.1) and determined to be safe, tolerable, and supportive of escalation.

Amended Text:

Escalation to the next higher single **dose** or to Part 2 will only proceed after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and the investigator at the Dose Escalation Committee meeting (Section 10.8.1) and determined to be safe, tolerable, and supportive of escalation.

New Section 4.5.5, GSK3389404 and Nucleos(t)ides

Rationale for change: To provide supporting data to update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Not applicable

Amended Text:

GSK3389404 is unlikely to be a victim or perpetrator of drug-drug interactions when administered with nucleos(t)ides due to their divergent absorption, distribution, metabolism, and excretion pathways.

Victim drug-drug interactions:

GSK3389404 is taken up into the liver by target mediated endocytosis and into the kidney by micropinocytosis, both routes that are not inhibited by small molecule drugs such as tenofovir, entecavir, lamivudine, adefovir and telbivudine. Furthermore GSK3389404 is metabolized by endogenous endonucleases, which are not inhibited by these 5 drugs.

Perpetrator drug-drug interactions:

Tenofovir, entecavir, lamivudine, adefovir and telbivudine are predominantly renally eliminated from systemic circulation [Lamivudine, 2002; Kearney, 2004; Adefovir, 2012; Telbivudine, 2013; Entecavir, 2015]. 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].

In a recent study, a model compound of 2'-O-(2-methoxyethyl) modified antisense oligonucleotide was shown to be neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2 [Yu, 2016]. Therefore, GSK3389404 or the primary tissue metabolite ISIS 505358 that was shown to be extensively distributed into the kidney in non-clinical studies, is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

Section 4.6 Benefit:Risk Assessment

Rationale for change: To make minor edits for clarity

Original Text

GlaxoSmithKline Document Number 2015N236049_02

Amended Text

~~GlaxoSmithKline Document Number 2015N236049_02~~

Section 4.6.2 Benefit Risk Summary, Paragraph 3, Number 2

Rationale for change: To make minor edits for clarity.

Original Text:

2. During Part 1 (SAD), dosing is sequential and subjects are housed in a research unit and closely monitored for at least 24 hours. Following discharge from the study site on Day 2 or 3, subjects have extended follow-up out to 60 days post-dose to assess safety. A low starting dose, based on the fold coverage to mean NOAEL in the 13-week monkey toxicity study, was selected for the initial dose in Part 1.

Amended Text:

2. During Part 1 (SAD), dosing is sequential and subjects are ~~housed in a research unit and~~ closely monitored for at least ~~24~~**48** hours **post-dose**. ~~Following discharge from the study site on Day 2 or 3, s~~**Subjects** have extended follow-up out to 60 days post-dose to assess safety. A low starting dose, based on the fold coverage to mean NOAEL in the 13-week monkey toxicity study, was selected for the initial dose in Part 1.

Section 5, Selection of Study Population and Withdrawal Criteria, Paragraph 1, Sentence 1

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

This first-in-patient study will enroll adult male and female subjects in the immune active phase of HBV infection who are not currently receiving HBV treatment.

Amended Text:

This first-in-patient study will enroll adult male and female subjects in the immune active phase of HBV infection who are not currently receiving HBV treatment **(Part 1) or who are currently on a stable nucleos(t)ide regimen (Part 2)**.

Section 5, Selection of Study Population and Withdrawal Criteria, Paragraph 1, New Sentence 3

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Not applicable

Amended Text:

Subjects who are on a stable nucleos(t)ide regimen are characterized by ALT levels less than or equal to the upper limit of normal (ULN) and have suppressed HBV DNA, defined as HBV DNA less than or equal to the lower limit of quantification (LLOQ).

Section 5, Selection of Study Population and Withdrawal Criteria, Paragraph 2

Rationale for change: To make minor edits for clarity

Original Text

GlaxoSmithKline Document Number 2015N236049_02

Amended Text

~~GlaxoSmithKline Document Number 2015N236049_02~~

Section 5.1, Inclusion Criteria, Number 5

Rationale for change: To make minor edits for clarity- to allow lab to use either serum or plasma to analyze HBsAg.

Original Text:

5. Documented chronic HBV infection, defined as positive serum HBsAg ≥6 months prior to screening.

Amended Text:

5. Documented chronic HBV infection, defined as positive **plasma or** serum HBsAg ≥6 months prior to screening.

Section 5.1, Inclusion Criteria, Number 6

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

6. Treatment naive or have had prior treatment with interferon (pegylated or non-pegylated) that must have ended at least 12 months prior to the Baseline visit (Day 1 pre-dose) and/or nucleos(t)ide analogue therapy that must have ended at least 6 months prior to the Baseline visit.

Amended Text:

6. **Subject with HBV treatment history as follows:**

   a. Part 1: Treatment naive or have had prior treatment with interferon (pegylated or non-pegylated) that must have ended at least 12 months prior to the Baseline visit (Day 1 pre-dose) and/or nucleos(t)ide analogue therapy that must have ended at least 6 months prior to the Baseline visit.

   b. Part 2: Subjects with CHB receiving stable nucleos(t)ide analogue therapy, defined no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study.

Section 5.1, Inclusion Criteria, Number 7

Rationale for change: To make minor edits for clarity- to allow lab to use either serum or plasma to analyze HBV DNA.

Original Text:

7. Plasma HBV DNA concentration:

    a. ≥20,000 IU/mL for HBeAg-positive subject

    b. ≥2000 IU/mL for HBeAg-negative subjects

Amended Text:

7. Plasma **or serum** HBV DNA concentration:

    a. Part 1:

        i. ≥20,000 IU/mL for HBeAg-positive subject

        ii. ≥2000 IU/mL for HBeAg-negative subjects

    b. Part 2: HBV DNA must be adequately suppressed, defined as plasma or serum HBV DNA <LLOQ.

Section 5.1, Inclusion Criteria, Number 8

Rationale for change: To make minor edits for clarity- to allow lab to use either serum or plasma to analyze HBsAg.

Original Text:

8. Serum HBsAg concentration >50 IU/mL.

Amended Text:

8. **Plasma or s**erum HBsAg concentration >50 IU/mL.

Section 5.1, Inclusion Criteria, Number 9

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced. To make minor edits for clarity.

Original Text:

9. Alanine aminotransferase (ALT) concentration >60 U/L for males, >38 U/L for females, and ≤10 X the upper limit of normal (ULN).

Amended Text:

9. Alanine aminotransferase (ALT) concentration**:**

   a. **Part 1: ALT** >60 U/L for males, >38 U/L for females, and ≤10 X ~~the upper limit of normal (~~ULN~~)~~.

   b. **Part 2: ALT ≤ULN**

Section 5.2, Exclusion Criteria, Number 1b and addition of 1c

Rationale for change: To make minor edits for clarity on the type of hypertension that will be excluded- the exclusion criteria was designed to exclude patients with significant cardiac or renal disease, not controlled hypertension.

Original text:

1. Medical history
   a. History of or active diagnosis of liver disease other than CHB, such as autoimmune hepatitis, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, hemochromatosis, or liver failure.
   b. History or other clinical evidence of hypertension, significant or unstable cardiac disease (e.g., prolonged QT syndrome [torsade de pointes], angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease and/or clinically significant ECG abnormalities).
   c. History of, or active diagnosis of, primary or secondary renal disease (e.g., renal disease secondary to diabetes, hypertension, vascular disease, etc.).
   d. History of extrahepatic disorders possibly related to HBV immune complexes (e.g., glomerulonephritis and polyarteritis nodosa).
   e. History of bleeding diathesis or coagulopathy.
   f. History of or suspected presence of vasculitis.
   g. History of Gilbert's Syndrome.
   h. History of malignancy within the past 5 years with the exception of specific cancers that are cured by surgical resection (e.g., skin cancer), subjects under evaluation for possible malignancy are not eligible.

Amended text:

1. Medical history
    a. History of or active diagnosis of liver disease other than CHB, such as autoimmune hepatitis, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, hemochromatosis, or liver failure.
    b. History or other clinical evidence of ~~hypertension,~~ significant or unstable cardiac disease (e.g., prolonged QT syndrome [torsade de pointes], angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease and/or clinically significant ECG abnormalities).
    c. Uncontrolled or history of difficult to control hypertension.
    d. History of, or active diagnosis of, primary or secondary renal disease (e.g., renal disease secondary to diabetes, hypertension, vascular disease, etc.).
    e. History of extrahepatic disorders possibly related to HBV immune complexes (e.g., glomerulonephritis and polyarteritis nodosa).
    f. History of bleeding diathesis or coagulopathy.
    g. History of or suspected presence of vasculitis.
    h. History of Gilbert's Syndrome.
    i. History of malignancy within the past 5 years with the exception of specific cancers that are cured by surgical resection (e.g., skin cancer), subjects under evaluation for possible malignancy are not eligible.

Section 5.4.1, Liver Chemistry Stopping Criteria, Paragraph 2

Rationale for change: To make minor edits for clarity

Original Text:

Table 5 provides guidance for liver stopping criteria for subjects with baseline ALT less than the ULN and for subjects with elevated baseline ALT.

Amended Text:

Table 5 provides guidance for liver stopping criteria for subjects with baseline ALT less than **or equal to** the ULN and for subjects with elevated baseline ALT.

Section 5.4.1, Liver Chemistry Stopping Criteria, Paragraph 3

Rationale for change: To make minor edits for clarity. To reduce complexity and visit burden for subjects.

Original Text:

Eligible subjects should have an elevated ALT at screening as specified in Section 5.1. However, the screening ALT may differ from the baseline ALT. Baseline ALT will be measured prior to dosing on Day 1, but results will not be available from the central laboratory until after the subject has already been dosed

Amended Text:

Eligible subjects **in Part 1** should have an elevated ALT at screening as specified in Section 5.1. Baseline ALT will be measured prior to dosing on Day 1, but results will not be available from the ~~central~~ laboratory until after the subject has already been dosed

Section 6.1, Investigational Product and Other Study Treatment, Table 6, Row 8

Rationale for change: To make minor edits for clarity. Normal Saline is not always provided by study site.

Original Text:

Manufacturer/Source of Procurement:	GSK Global Manufacturing and Supply, Parma (Italy)	Sourced locally at study site

Amended Text:

Manufacturer/Source of Procurement:	GSK Global Manufacturing and Supply, Parma (Italy)	~~Sourced locally at study site~~ **Locally sourced normal saline**

Section 6.1, Investigational Product and Other Study Treatment, Table 7, Row 1 and footnote 1and footnote 2

Rationale for change: To make minor edits for clarity

Original Text:

Total Dose[1]	**Total Volume to Administer**[2]
30 mg or placebo	0.30 mL
60 mg or placebo	0.60 mL
120 mg or placebo	1.2 mL
240 mg or placebo	2.4 mL

1. Total dose may change based on safety and pharmacokinetic data from preceding cohort(s)
2. If a change in total dose is warranted, total volume to administer (mL) = dose (mg)/100

Amended Text:

~~**Total** **Dose**~~[1]	~~**Total** **Volume to Administer**~~[2]
30 mg or placebo	0.30 mL
60 mg or placebo	0.60 mL
120 mg or placebo	1.2 mL
240 mg or placebo	2.4 mL

1. ~~Total d~~ **D**ose may change based on safety and pharmacokinetic data from preceding cohort(s)
2. If a change in ~~total~~ dose is warranted, ~~total~~ volume to administer (mL) = dose (mg)/100

Section 6.3, Planned Dose Adjustments, Paragraph 1, Bullet 1, Sub-bullet 3

Rationale for change: To make minor edits for clarity

Original Text:

- In the case of undetectable or extremely low concentrations following the first dose (e.g., if the majority of PK samples are below the lower limit of quantification), a more than 3-fold increase in dose may be considered for the next dose level;

Amended Text

- In the case of undetectable or extremely low concentrations following the first dose (e.g., if the majority of PK samples are below ~~the lower limit of quantification~~ **LLOQ**), a more than 3-fold increase in dose may be considered for the next dose level;

Section 6.6, Packaging and Labeling, Paragraph 2

Rationale for change: To make minor edits for clarity

Original Text:

A placebo to match GSK3389404 solution for injection will be site sourced normal saline solution.

Amended Text:

A placebo to match GSK3389404 solution for injection will be ~~site~~ **locally**-sourced normal saline solution.

Section 6.10, Treatment after the End of the Study, Paragraph 1

Rationale for change: To make minor edits for clarity. To allow for exceptional circumstances that may require GSK to provide treatment options for subjects.

Original Text:

Subjects will not receive any additional treatment from GSK after completion of the study.

Amended Text:

~~Subjects will not receive any additional treatment from GSK after completion of the study.~~

Section 6.10, Treatment after the End of the Study, Paragraph 2, Bullets 1 and 2

Rationale for change: To make minor edits for clarity. To allow for exceptional circumstances that may require GSK to provide treatment options for subjects.Original Text:

- In Part 1, subjects with CHB may be evaluated by the investigator for initiation of standard of care therapy after the final Follow-up visit (Day 60). The study sponsor will not be responsible for providing standard of care.
- In Part 2, subjects with CHB may be evaluated by the investigator for initiation of standard of care therapy during the study as appropriate based on evidence of CHB exacerbation or at any time after Day 113. The study sponsor will not be responsible for providing standard of care.

Amended Text:

- In Part 1, subjects with CHB may be evaluated by the investigator for initiation of standard of care therapy after the final Follow-up visit (Day 60~~). The study sponsor will not be responsible for providing standard of care.~~
- In Part 2, subjects with CHB may ~~be evaluated by the investigator for initiation of standard of care therapy during the study as appropriate based on evidence of CHB exacerbation or at any time after Day 113. The study sponsor will not be responsible for providing standard of care~~ **discuss post-study care with the investigator**.

Section 6.11.1, Meals and Dietary Restrictions, Paragraph 2, Bullet 1, Bullet 2 and sub-bullet

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

During the in-house stay in Part 1, subjects will be restricted to meals and beverages provided at the study site.

- On Day 1, a morning snack (not full meal) will be provided after dosing and completion of morning study procedures. Lunch will be provided approximately 4 hours post-dose, dinner will be provided approximately 9 hours post-dose, and an evening snack may be available until 22:00 hours.
- On Day 2, breakfast will be provided after completion of morning procedures/prior to discharge from the study site.
    - If subjects decide to stay in-house through Day 3, lunch will be provided approximately 4 hours after the breakfast, dinner will be provided approximately 9 hours after the breakfast, and an evening snack may be available until 22:00 hours.

Amended Text:

Admission to the study site is optional. If subjects opt to stay ~~During the~~ in-house ~~stay~~ in Part 1, subjects will be restricted to meals and beverages provided at the study site.

- On Day 1, a ~~morning~~ snack (not full meal) will be provided after dosing and completion of ~~morning~~ study procedures. Lunch will be provided approximately 4 hours post-dose~~,~~**. If subjects are still on-site,** dinner will be provided approximately 9 hours post-dose~~,~~ and an evening snack will be available until 22:00 hours.
- On Day 2, breakfast**, lunch, and dinner may** ~~will~~ be provided ~~after completion of morning procedures/prior to discharge from the study site~~.
    - ~~If subjects decide to stay in-house through Day 3, lunch will be provided approximately 4 hours after the breakfast, dinner will be provided approximately 9 hours after the breakfast, and an evening snack will be available until 22:00 hours~~ **Subjects may be discharged at any time on Day 2**.
    - **An evening snack will be available until 22:00 hours.**

Section 6.12.1, Permitted Medications and Non-Drug Therapies, Paragraph 1, Sentence 1

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced

Original Text:

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 6.12.2).

Amended text:

In Part 2, required medication includes nucleos(t)ide agents such as tenofovir, entecavir, lamivudine, adefovir and telbivudine. Other concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 6.12.2).

Section 6.12.2, Prohibited Medications and Non-Drug Therapies, Entire section

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced and impact on concomitant medications.

Original Text:

- Interferon (pegylated or non-pegylated) from 12 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).
- Nucleos(t)ide analogue therapy from 6 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).
- Immunosuppressing drug (e.g., prednisone) use >2 weeks duration from 3 months prior to Screening through the final Follow-up visit (see Exclusion Criterion 11, Section 5.2).
- Oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit (see Exclusion Criterion 11, Section 5.2).

Amended Text:

The following concomitant medications are not permitted **during Part 1**:

- Interferon (pegylated or non-pegylated) from 12 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).
- Nucleos(t)ide analogue therapy from 6 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).

The following concomitant medications are not permitted during Part 1 and Part 2:

- Immunosuppressing drug (e.g., prednisone) use >2 weeks duration from 3 months prior to Screening through the final Follow-up visit (see Exclusion Criterion 11, Section 5.2).
- Oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit (see Exclusion Criterion 16, Section 5.2).

Section 7.1, Table 8, Header Row

Rationale for change: To make minor edits for clarity.

Original Text:

Assessment	**Screening**

Amended Text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**

Section 7.1, Table 8, Column 1, Rows 19 and 20

Rationale for change: To make minor edits for clarity

Original Text:

Hepatitis B screen (quantitative HBsAg; plasma)
Hepatitis B profile (quantitative HBV DNA, HBeAg; plasma)

Amended Text:

Hepatitis B screen (~~quantitative~~ HBsAg; plasma **or serum**)
Hepatitis B profile (~~quantitative~~ HBV DNA, HBeAg; plasma **or serum**)

Section 7.1, Table 9

Rationale for change: To reduce complexity and visit burden for subjects. To make minor edits for clarity- to allow for both quantitative and/or qualitative testing

Original Text (on next page):

Assessments	Day-1[1]	Day 1											
				Post Dose in Hours (h)									
		Pre-dose[1]	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	9 h	12 h
Inclusion and exclusion criteria	X												
Admission to study site[1]	(X[1])	X[1]											
Randomization[2]		X											
Study treatment dosing[3]			X										
Meals[4]	X								X			X	
Safety Assessments													
AE/SAE review[5]	←						Continuous						→
Concomitant medication review	←						Continuous						→
Brief physical exam	X												
Vital signs[6]	X	X			X		X		X		X		X
Holter		X	X	X	X	X	X	X	X	X			
12-lead ECG[7]	X	X					X		X				X
Injection site reactions[8]			X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments													
Drug/Alcohol screen[9]	X												
Pregnancy test (as appropriate) [9,10]	X												
Hematology/Chemistry/Urinalysis[9,11,12]	X	X											
Urine ACR[9,12,13]	X												
Complement (C3/C4)	X						X		X				X
PT, INR, aPTT[9]	X						X		X				X
hs-CRP[9]	X												
PK sampling[14]		X		X	X	X	X	X	X	X	X		X
Archived serum and plasma samples[15]		X											
Quantitative HBsAg and HBV DNA	X												X
Quantitative HBeAg[16]	X												X

Assessments	Day-1[1]	Day 1											
				Post Dose in Hours (h)									
		Pre-dose[1]	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	9 h	12 h
HBV genotype/phenotype[17]	X												X

Amended Text:

Assessments	Day-1[1]	Day 1											
				Post Dose in Hours (h)									
		Pre-dose[12]	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	~~9 h~~	~~12 h~~
Inclusion and exclusion criteria	~~X~~	**X**											
Admission to study site[1]	(X[1])	**(X)[1]**											
Discharge from study site[1]													~~(X)~~
Randomization[2]		X											
Study treatment dosing[3]			X										
Meals[4]	~~X~~								X			~~X~~	
Safety Assessments													
AE/SAE review[5]	← Continuous →												
Concomitant medication review	← Continuous →												
Brief physical exam	~~X~~	**X**											
Vital signs[6]	~~X~~	X			X		X		X		X		~~X~~
Holter		X	X	X	X	X	X	X	X	X			
12-lead ECG[7]	~~X~~	X					X		X				~~X~~
Injection site reactions[8]			X	X	X	X	X	X	X	X	X	~~X~~	~~X~~
Laboratory Assessments													
~~Drug/Alcohol screen~~[9]	~~X~~												

Assessments	Day-1[1]	Day 1											
				Post Dose in Hours (h)									
		Pre-dose[12]	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	~~9 h~~	~~12 h~~
Pregnancy test (as appropriate) [9,10]	~~X~~	**X**											
Hematology/Chemistry/Urinalysis[9, 10,11,12]	~~X~~	**X**											
Urine ACR[9,11,12,13]	~~X~~	**X**											
Complement (C3/C4)	~~X~~	**X**					X		X				~~X~~
PT, INR, aPTT[9]	~~X~~	**X**					X		X				~~X~~
hs-CRP[9]	~~X~~	**X**											
PK sampling[14,13]		**X**		X	X	X	X	X	X	X	X		~~X~~
Archived serum and plasma samples[15,14]		**X**											
~~Quantitative~~ HBsAg and HBV DNA	~~X~~	**X**											~~X~~
~~Quantitative~~ HBeAg[16,15]	~~X~~	**X**											~~X~~
HBV genotype/phenotype[17,16]	~~X~~	**X**											~~X~~

Section 7.1, Table 9, Footnotes 1, 4, 7, 9-17

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

1. Day -1 admission is optional based on laboratory capabilities and study site/subject preference. The study site/subject may use Day -1 as an outpatient visit for assessments and blood sample collection. If the subject is willing to arrive early and the site is capable (early admission available, critical laboratory result turn-around available prior to randomization), subjects may be admitted on Day 1 with all Day -1 assessments conducted pre-dose.

4. On Day 1, subjects may receive a morning snack (not full meal) after completion of morning study procedures and post-dose, prior to lunch. Lunch will be approximately 4 hours (±1 hour) dosing and dinner approximately 9 hours (±1 hour) after dosing. An evening snack (optional) may be provided until 22:00 hours

7. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi supine or supine position and all other ECGs to be measured in duplicate.

9. Laboratory assessment results are required before randomization

10. Female subjects at screening and pre-dose: serum hCG pregnancy test; All other time points: serum hCG or urine pregnancy test.

11. Samples may be collected on Day -1 and/or pre-dose Day 1. At least one set of samples must be obtained after an overnight fast (at least 8 hours) and before breakfast.

12. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.

13. Collect first morning urine void sample for ACR assessment while subjects are in study site.

14. Plasma PK samples to be collected pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible). Post-dose PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.

15. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

16. HBeAg-positive subjects only.

17. HBV Genotype/Phenotype sample to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

Amended Text:

~~1. Day -1 admission is optional based on laboratory capabilities and study site/subject preference. The study site/subject may use Day -1 as an outpatient visit for assessments and blood sample collection. If the subject is willing to arrive early and the site is capable (early admission available, critical laboratory result turn-around available prior to randomization), subjects may be admitted on Day 1 with all Day -1 assessments conducted pre-dose.~~ ~~1.~~ **Admission to the study site is optional. Subjects admitted on Day -1 may be discharged after completion of all protocol specified procedures on Day 1, 8-hour time point, with instructions to return for outpatient visits (Days 3, 8, 15, 22, 30, and 60).**

4. On Day 1, subjects may receive a morning snack (not full meal) after completion of morning study procedures and post-dose, prior to lunch. Lunch will be approximately 4 hours (±1 hour) dosing. **If subjects are still on site,** ~~and~~ dinner **will be provided** approximately 9 hours (±1 hour) after dosing. An evening snack (optional) may be provided until 22:00 hours

7. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi supine or supine position and **duplicate at** all other **measurement time points**~~ECGs to be measured in duplicate~~.

~~9. Laboratory assessment results are required before randomization~~

~~10.~~ **9.** Female subjects at screening and pre-dose: serum hCG pregnancy test; All other time points: serum hCG or urine pregnancy test.

~~11.~~**10.** ~~Samples may be collected on Day -1 and/or pre-dose Day 1. At least one set of samples~~ **Sample** must be obtained after an overnight fast (at least 8 hours) and before breakfast.

~~12.~~**11** The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.

~~13.~~**12** Collect first morning urine void sample for ACR assessment while subjects are in study site.

~~14.~~**13** Plasma PK samples to be collected pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible). Post-dose PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.

~~15.~~**14** Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

~~16.~~**15** HBeAg-positive subjects only.

~~17.~~**16** HBV Genotype/Phenotype sample to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

Section 7.1, Table 10

Rationale for change: To reduce complexity and visit burden for subjects. To make minor edits for clarity- to allow for both quantitative and/or qualitative testing.

Original Text:

	Day 2			**DAY 3**	**Day 8**	**Day 15**	**Day 22**	**Day 30**	**Day 60**	
	Post Dose in Hours (h)				**(±1 day)**	**(±1 day)**	**(±1 day)**	**(±1 day)**	**(±1 day)**	**ET**
Assessment	**24 h**	**28 h**	**33 h**	**48 h (±8 h)**						
Meals[1]	X	(X)[1]	(X)[1]	(X)[1]						
Discharge from study site[2]	(X)[2]			(X)[2]						
Outpatient visits				(X)[2]	X	X	X	X	X	X
Safety Assessments										
AE/SAE review[3]	← Continuous →									
Concomitant medication review	← Continuous →									
Brief physical exam					X			X	X	X
Vital signs[4]	X			X	X			X		X
12-lead ECG[5]	X			X	X			X		X
Injection site reactions[6]	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Pregnancy test (as appropriate)[7]					X			X	X	X
Hematology/Chemistry/Urinalysis[8,9]	X			X	X			X	X	X
Urine ACR[9,10]	X				X			X	X	X
Complement (C3/C4)	X			X	X			X		X
PT, INR, aPTT	X			X	X			X		X
hs-CRP	X			X	X			X		X
PK sampling[11]	X			X	X			X		X
Archived serum and plasma samples[12]	X			X	X			X		X

	Day 2			DAY 3	Day 8	Day 15	Day 22	Day 30	Day 60	
	Post Dose in Hours (h)				(±1 day)	(±1 day)	(±1 day)	(±1 day)	(±1 day)	ET
Assessment	**24 h**	**28 h**	**33 h**	**48 h (±8 h)**						
Quantitative HBsAg, HBV DNA	X			X	X	X	X	X	X	X
Quantitative HBeAg[13]	X			X	X	X	X	X	X	X
HBV genotype/phenotype[14]	X			X	X	X	X	X	X	X

Amended Text:

	Day 2			DAY 3	Day 8	Day 15	Day 22	Day 30	Day 60	
	Post Dose in Hours (h)				(±1 day)	(±1 day)	(±1 day)	(±1 day)	(±1 day)	ET
Assessment	~~**24 h**~~	~~**28 h**~~	~~**33 h**~~	**48 h (±8 h)**						
Meals[1]	X	~~(X)~~[1]	~~(X)~~[1]	(X)[1]						
Discharge from study site[2]	(X)[2]			(X)[2]						
Outpatient visits				(X)[2]	X	X	X	X	X	X
Safety Assessments										
AE/SAE review[3]	←				Continuous					→
Concomitant medication review	←				Continuous					→
Brief physical exam					X			X	X	X
Vital signs[4]	~~X~~			X	X			X		X
12-lead ECG[5]	~~X~~			X	X			X		X
Injection site reactions[6]	~~X~~	~~X~~	~~X~~	X	X	X	X	X	X	X
Laboratory Assessments										
Pregnancy test (as appropriate)[7]					X			X	X	X
Hematology/Chemistry/Urinalysis[8,9]	~~X~~			X	X			X	X	X
Urine ACR[9,10]	~~X~~				X			X	X	X
Complement (C3/C4)	~~X~~			X	X			X		X
PT, INR, aPTT	~~X~~			X	X			X		X

	Day 2			**DAY 3**	**Day 8**	**Day 15**	**Day 22**	**Day 30**	**Day 60**	
	Post Dose in Hours (h)				**(±1 day)**	**(±1 day)**	**(±1 day)**	**(±1 day)**	**(±1 day)**	**ET**
Assessment	~~**24 h**~~	~~**28 h**~~	~~**33 h**~~	**48 h (±8 h)**						
hs-CRP	~~X~~			X	X			X		X
PK sampling[11]	~~X~~			X	X			X		X
Archived serum and plasma samples[12]	~~X~~			X	X			X		X
~~Quantitative~~ HBsAg, HBV DNA	~~X~~			X	X	X	X	X	X	X
~~Quantitative~~ HBeAg[13]	~~X~~			X	X	X	X	X	X	X
HBV genotype/phenotype[14]	~~X~~			X	X	X	X	X	X	X

Section 7.1, Table 10, Footnotes 1 and 2

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

1. On Day 2, breakfast is provided after completion of morning procedures/prior to discharge. If subjects choose to stay in-house through Day 3, then on Day 2, lunch will also be served approximately 4 hours (±1 hour) after the breakfast, dinner will be served approximately 9 hours (±1 hour) after the breakfast, and an evening snack (optional) may be provided until 22:00 hours. If subjects choose to stay in-house through Day 3, they will be offered a meal (e.g., bagged or canteen) after completion of all study procedures and prior to discharge on Day 3.

2. Discharge from the study site may occur after completion of all protocol specified procedures on Day 2 with instructions to return for outpatient visits (Days 3. 8, 15, 22, 30, and 60). If subjects prefer, they may stay in-house until all Day 3 assessments are completed.

Amended Text:

1. On Day 2, breakfast**, lunch, and dinner may be** ~~is~~ provided**.** ~~after completion of morning procedures/prior to discharge.~~ If subjects choose to stay in-house through Day 3, then on Day 2, lunch will also be served approximately 4 hours (±1 hour) after the breakfast, dinner will be served approximately 9 hours (±1 hour) after the breakfast, and an evening snack (optional) may be provided until 22:00 hours. If subjects choose to stay in-house through Day 3, they will be offered a meal (e.g., bagged or canteen) after completion of all study procedures and prior to discharge on Day 3.

2. **Subjects may be** ~~D~~**d**ischarge**d** ~~from the study site may occur after completion of all protocol specified procedures~~ **at any time** on Day 2 with instructions to return for outpatient visits (Days 3. 8, 15, 22, 30, and 60). If subjects prefer, they may stay in-house until all Day 3 assessments are completed.

Section 7.1, Table 11, Table 13, and Table 15 Rows 20 through 25

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

PK sampling[11,12]	X[11,12]	X[11]	X[11]	X[11]	X[11,12]	X[11]	X[11]	X[11]	X[11,12]	X[11]	X[11]	X[11]	X[11]
Archived serum and plasma samples[13]	X				X				X				X
Quantitative HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HBeAg[14]	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotype/phenotype[15]	X		X		X		X		X		X		X
Meal[16]	X	X	X	X	X	X	X	X	X	X	X	X	X

Amended Text:

PK sampling[11,~~12~~]	X[11,12]	~~X[11]~~	~~X[11]~~	~~X[11]~~	X[11,12]	~~X[11]~~	~~X[11]~~	~~X[11]~~	X[11,12]	~~X[11]~~	~~X[11]~~	~~X[11]~~	~~X[11]~~
Archived serum and plasma samples[~~13~~**12**]	X				X				X				X
~~Quantitative~~ HBsAg and HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X
~~Qualitative~~ HBeAg[~~14~~**13**]	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotype/phenotype[~~15~~**14**]	X		X		X		X		X		X		X
HBsAb	**X**												**X**
Meal[~~16~~**15**]	X	X	X	X	X	X	X	X	X	X	X	X	X

Section 7.1, Table 11, Table 13, and Table 15, New abbreviation footnote

Rationale for change: addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

Not applicable

Amended Text:

HBsAb = hepatitis B virus surface antibody

Section 7.1, Tables 11, 13, and 15 Footnotes 1, 2, and 5

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

1. Subjects randomized to GSK3389404 or placebo on Day 1 prior to dosing, but only after critical assessments are performed to ensure subject eligibility.

2. Study treatment will be administered as subcutaneous injection(s) in the morning following an overnight fast of at least 8 hours and subsequent to the laboratory assessments and other study assessments conducted prior to dosing.

5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and all other ECGs to be measured in duplicate.

Amended Text:

1. Subjects randomized to GSK3389404 or placebo on Day 1 prior to dosing~~, but only after critical assessments are performed to ensure subject eligibility~~.

2. Study treatment will be administered as subcutaneous injection(s) in the morning following an overnight fast of at least 8 hours and subsequent to the laboratory ~~assessments~~ **collection** and other study assessments conducted prior to dosing.

5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and **duplicate at all other** ~~ECGs to be measured in duplicate~~ **measurement time points**.

Section 7.1, Table 11, Table 13, and Table 15, Footnotes 11 through 16

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

11. Collect plasma PK samples on all days indicated. On dosing days, collect PK samples pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible). On Day 85, collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded.

12. On extended PK/dosing days (Days 1, 29, and 57), additional PK samples will be collected at 1, 2, 3, and 4 hours post-dose. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.

13. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

14. HBeAg-positive subjects only.

15. HBV Genotype/Phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

16. Subjects will be offered a meal (e.g., bagged or canteen) after completion of all study procedures.

Amended Text:

~~11. Collect plasma PK samples on all days indicated. On dosing days, collect PK samples pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible). On Day 85, collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded.~~

~~12~~**11**. On extended PK/dosing days (Days 1, 29, and 57), ~~additional~~ PK samples will be collected at **pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible) and** at 1, 2, **and** 3~~, and 4~~ hours post-

dose. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.

~~13~~**12**. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

~~14~~**13**. HBeAg-positive subjects only.

~~15~~**14**. HBV Genotype/Phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.

~~16~~**15**. Subjects will be offered a meal (e.g., bagged or canteen) after completion of all study procedures.

Section 7.1, Table 12, Table 14, and Table 16, Row 18

Rationale for change: To reduce complexity and visit burden for subjects.

Original Text:

PK sampling[9]	X	X	X	X	X	X

Amended Text:

PK sampling[9]	~~X~~	~~X~~	~~X~~	~~X~~	X	X

Section 7.1, Table 12, Table 14, and Table 16, Column 1, Rows 20 and 21

Rationale for change: To make minor edits for clarity- to allow for both quantitative and/or qualitative testing

Original Text:

Quantitative HBsAg and HBV DNA
Quantitative HBeAg[11]

Amended Text:

~~Quantitative~~ HBsAg and HBV DNA
~~Quantitative~~ HBeAg[11]

Section 7.1, Table 12, Table 14, and Table 16, New Row 23

Rationale for change: addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

Meal[13]	X	X	X	X	X	X

Amended Text:

HBsAb					**X**	**X**
Meal[13]	X	X	X	X	X	X

Section 7.1, Table 12, Table 14, and Table 16, New abbreviation footnote

Rationale for change: addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

Not applicable

Amended Text:

HBsAb = hepatitis B virus surface antibody

Section 7.1, Table 12, Table 14, and Table 16, Footnote 9

Rationale for change: To make minor edits for clarity

Original Text:

9. The exact time of each PK blood collection should be recorded.

Amended Text:

9. **On PK days (Day 169 / Early Termination), collect the PK sample after completion of vital sign assessments.** The exact time of each PK blood collection should be recorded.

Section 7.1, Table 16, Row 10

Rationale for change: To make minor edits for clarity- to correct a clerical error in not including assessment

Original Text:

Injection site reactions[4]						

Amended Text:

Injection site reactions[4]	**X**	**X**	**X**	**X**	**X**	**X**

Section 7.2, Screening and Critical Baseline Assessments, Paragraph 2, Bullet 3

Rationale for change: To make minor edits for clarity

Original Text:

- Procedures conducted as part of the subject's routine clinical management (qualitative HBsAg, liver biopsy, Fibroscan, APRI, or FibroSure) and obtained prior to signing of informed consent may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the inclusion/exclusion criteria listed in Section 5.

Amended Text:

- Procedures conducted as part of the subject's routine clinical management (~~qualitative~~ HBsAg, liver biopsy, Fibroscan, APRI, or FibroSure) and obtained prior to signing of informed consent may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the inclusion/exclusion criteria listed in Section 5.

Section 7.3.8, Clinical Safety Laboratory Assessments, Paragraph 4

Rationale for change: To make minor edits for clarity- based on decision that this information was not needed in electronic case report form (CRF) as information would be provided in narratives/reports.

Original Text:

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE, AE, or dose modification) the results must be recorded in the CRF.

Amended Text:

~~If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE, AE, or dose modification) the results must be recorded in the CRF.~~

Section 7.3.8, Clinical Safety Laboratory Assessments, Paragraph 5, Sentence 3

Rationale for change: To make minor edits for clarity- based on decision that this information was not needed in electronic case report form (CRF) as information would be provided in narratives/reports.

Original Text:

Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Amended Text:

~~Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.~~

Section 7.3.8, Clinical Safety Laboratory Assessments, Table 17, Row 7, Bullet 3 and new Bullet 4

Rationale for change: To make minor edits for clarity. Addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

- Quantitative HBsAg

Amended Text:

- ~~Quantitative~~ HBsAg
- **HBsAb**

Section 7.3.8, Clinical Safety Laboratory Assessments, Table 17, New abbreviation footnote

Rationale for change: Addition of new exploratory endpoint to assess GSK3389404 treatment outcomes in case seroconversion is seen in subjects with chronic hepatitis B

Original Text:

Not applicable

Amended Text:

HBsAb = hepatitis B virus surface antibody

Section 7.5, Efficacy, Paragraph 1, Sentence 1

Rationale for change: To make minor edits for clarity- to allow for both quantitative and/or qualitative testing

Original Text:

Blood samples for quantitative HBsAg will be collected as specified in the Time and Events Tables in Section 7.1.

Amended Text:

Blood samples for ~~quantitative~~ HBsAg will be collected as specified in the Time and Events Tables in Section 7.1.

Section 7.6 Biomarker(s)/Pharmacydynamic Markers, Paragraph 2, Sentence 3

Rationale for change: To make minor edits for clarity- to include additional analyses for biomarkers

Original Text:

Blood collection, processing, storage, and shipping details are provided in the SRM.

Amended Text:

The archive samples may also be used for studying biomarkers that may be affected by treatment, such as hepatitis B core-related antigen (HBcrAg) or indoleamine 2,3 dioxygenase (IDO). Blood collection, processing, storage, and shipping details are provided in the SRM.

New Section 7.7.1 HBV Resistance Mutation Monitoring

Rationale for change: To update the subject population in Part 2 from treatment naïve to treatment experienced; to define virologic breakthrough and processes should virologic breakthrough were to occur

Original Text:

Not applicable

Amended Text:

For Part 2, in subjects who are on a stable nucleos(t)ide regimen with adequate suppression of HBV DNA, defined as HBV DNA levels below the LLOQ:

Virologic breakthrough is defined as the occurrence of confirmed virologic breakthrough (e.g., HBV DNA becoming quantifiable after being below the LLOQ).

Plasma or serum HBV DNA levels for each subject will be measured throughout the study (see Time and Events Tables in Section 7.1). If evidence of virologic breakthrough is observed, subjects will be interviewed regarding treatment compliance and the concomitant usage of medication that might affect virus replication (e.g., corticosteroids), and other potentially relevant parameters.

Samples collected for viral genotyping and phenotyping may be used for HBV resistance mutation analysis where the viral genome will be DNA sequenced to determine whether mutations have occurred in the GSK3389404 binding region (and if applicable, whether any known nucleos(t)ide resistance mutations are present in the polymerase coding region).

Section 11 REFERENCES

Rationale for change: To make minor edits for clarity; additional references added

New references added

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Section 12.1 Appendix 1: Abbreviations and Trademarks, New abbreviations

Rationale for change: To make minor edits for clarity

Original Text:

Not applicable

Amended Text:

HBsAb	**hepatitis B virus surface antibody**
LLOQ	**lower limit of quantification**
OAT	**organic anion transporter**
OCT	**organic cation transporter**

Section 12.6.1, Introduction, New Paragraph 4

Rationale for change: To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

Not applicable

Amended Text:

The dosing regimens for selected treatment groups will be identical. For example, if 480 mg is selected for Part 2, other selected treatment groups will also be administered in a weekly and bi-weekly (every 2 weeks) dosing regimen.

Section 12.6.2, Statistical Modeling, Paragraph 1, Sentence 3

Rationale for change: To make minor edits for clarity.

Original Text:

Estimates for this model's parameters will be derived using the data generated within each treatment arm, i.e., this model will borrow degrees of freedom across active dose levels and regimens therefore providing higher power compared to pair-wise comparison given the small sample size of each treatment arm.

Amended Text:

Estimates for this model's parameters will be derived using the data generated within each treatment arm, i.e., this model will borrow degrees of freedom across active dose levels and regimens therefore providing higher power compared to pair-wise comparison given the small sample size of each treatment arm **and low expected response rate for placebo**.

Section 12.6.4, Scenarios for Testing, Paragraph 1, Sentence 1

Rationale for change: To make minor edits for clarity. To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Original Text:

It is assumed that 3 dose levels (60, 120, and 240 mg) each at 2 regimens (weekly and monthly) will be selected in Part 2.

Amended Text:

It is assumed that 3 dose levels (~~60,~~ 120, ~~and~~ 240**, and 480 mg**) each at 2 regimens (weekly and ~~monthly~~**bi-weekly**) will be selected in Part 2.

Section 12.64 and Section 12.6.5, Scenarios for Testing and Simulations, Table 18 through Table 28

Rationale for change: To make minor edits for clarity. To increase the maximum total monthly dose in Part 2 from 240 mg to 480 mg

Due to the updated scenarios for testing documented in Section 12.6.4, all simulation tables were updated.

12.7.2. Protocol changes for Amendment 02 (07-MAR-2017) from Protocol Amendment 01 (21-Feb-2017)

Protocol Amendment 2 replaces the protocol amendment 1 dated 21 Feb 2017 and applies to all study sites.

Protocol Amendment 2 is being implemented for the following reasons:

- To include patients with ALT less than 5X upper limit of normal (ULN) based on investigator feedback. Part 1 is a single dose administration to examine the safety and effect of viral biomarkers. Administration of a single dose of GSK3389404 is not considered likely to trigger a change in disease state or alter the benefit-risk assessment.

- To make minor edits for clarity and typographical errors.

LIST OF CHANGES

Title Page, Title

Rationale: Protocol Amendment 01 title did not match the original protocol title.

Original text:

A Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending and Multiple Doses of GSK3389404 in Chronic Hepatitis B Subjects

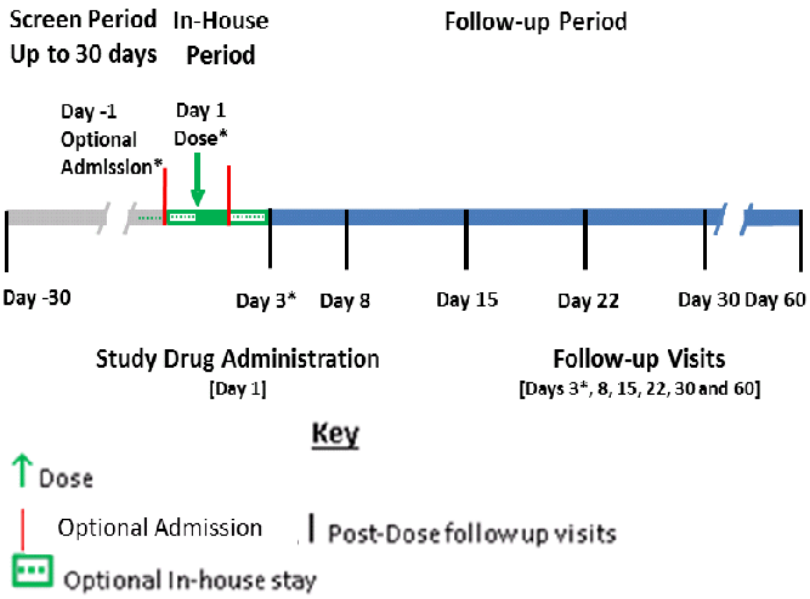
Amended text:

A Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending **Dose** and Multiple Doses of GSK3389404 in Chronic Hepatitis B Subjects

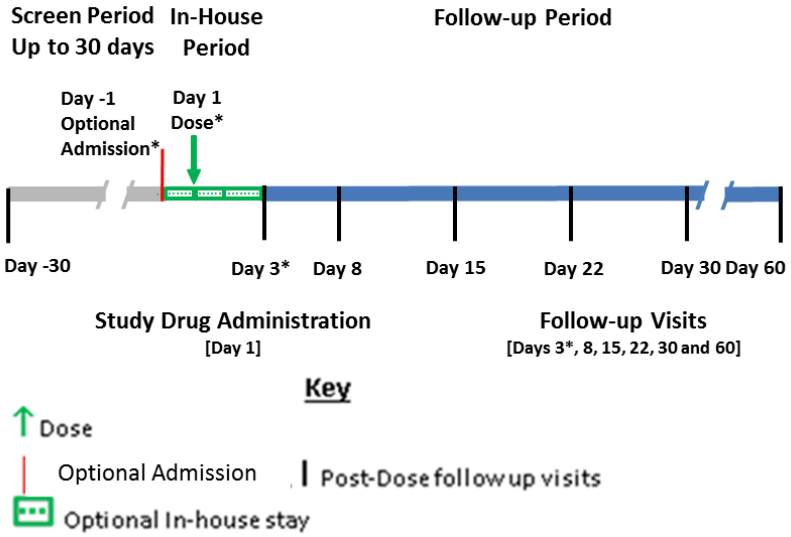
Section 4.2, Treatment Arms and Duration, Figure 3

Rationale for change: to edit figure for clarity, previous figure was unclear.

Original Figure:



Amended Figure:



Section 4.5.5, GSK3389404 and Nucleos(t)ides, last paragraph

Rationale for change: Minor edit for clarity

Original text:

In a recent study, a model compound of 2'-O-(2-methoxyethyl) modified antisense oligonucleotide was shown to be neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2 [Yu, 2016]. Therefore, although GSK404 was shown to be extensively

distributed into the kidney [Shemesh, 2016], GSK3389404 is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

Amended text:

In a recent study, a model compound of 2'-O-(2-methoxyethyl) modified antisense oligonucleotide was shown to be neither a substrate nor an inhibitor of OAT1, OAT3, OCT1 and OCT2 [Yu, 2016]. Therefore, although GSK**3389**404 was shown to be extensively distributed into the kidney [Shemesh, 2016], GSK3389404 is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

Section 5, Selection of Study Population and Withdrawal Criteria, Paragraph 1

Rationale for change: Part 1 is a single dose administration to examine the safety and effect of viral biomarkers. Based on investigator feedback, the recommendation is to include patients with ALT less than 5X upper limit of normal. Administration of a single dose of GSK3389404 is not considered likely to trigger a change in disease state or alter the benefit-risk assessment.

Original text:

This first-in-patient study will enroll adult male and female subjects in the immune active phase of HBV infection who are not currently receiving HBV treatment (Part 1) or who are currently on a stable nucleos(t)ide regimen (Part 2). The immune active phase, also referred to as HBeAg-positive or HBeAg-negative chronic hepatitis, is characterized by elevated alanine aminotransferase (ALT) levels, evidence of active hepatic inflammation, and HBV DNA levels greater than or equal to 2000 IU/mL. Subjects who are on a stable nucleos(t)ide regimen are characterized by ALT levels less than or equal to the upper limit of normal (ULN) and have suppressed HBV DNA, defined as HBV DNA less than or equal to the lower limit of quantification (LLOQ). The entry criteria for this study are designed to enroll subjects with CHB who do not have advanced liver fibrosis or cirrhosis, other concomitant liver diseases, co-infection, or other significant co-morbidities that would confound the safety monitoring and/or potentially put them at greater risk for treatment-related AEs. The ALT eligibility criteria are generally consistent with the International Liver Society guidelines (e.g., Asian Pacific Association for the Study of the Liver [Liaw, 2012], European Association for the Study of the Liver [EASL, 2012], American Association for the Study of Liver Diseases [Terrault, 2016]).

Amended text:

This first-in-patient study will enroll adult male and female subjects in **either the immune tolerant or** the immune active phase of HBV infection who are not currently receiving HBV treatment (Part 1) or who are currently on a stable nucleos(t)ide regimen (Part 2). **The immune tolerant phase is characterized by the absence of biochemical symptoms of the disease (i.e., elevated transaminase levels).** The immune active phase,

also referred to as HBeAg-positive or HBeAg-negative chronic hepatitis, is characterized by elevated alanine aminotransferase (ALT) levels, evidence of active hepatic inflammation, and HBV DNA levels greater than or equal to 2000 IU/mL. Subjects who are on a stable nucleos(t)ide regimen are characterized by ALT levels less than or equal to the upper limit of normal (ULN) and have suppressed HBV DNA, defined as HBV DNA less than or equal to the lower limit of quantification (LLOQ). The entry criteria for this study are designed to enroll subjects with CHB who do not have advanced liver fibrosis or cirrhosis, other concomitant liver diseases, co-infection, or other significant co-morbidities that would confound the safety monitoring and/or potentially put them at greater risk for treatment-related AEs. The ALT eligibility criteria are generally consistent with the International Liver Society guidelines (e.g., Asian Pacific Association for the Study of the Liver [Liaw, 2012], European Association for the Study of the Liver [EASL, 2012], American Association for the Study of Liver Diseases [Terrault, 2016]).

Section 5.1, Inclusion Criteria, Number 9

Rationale for change: To expand population to include subjects with normal ALT.

Original text:

Alanine aminotransferase (ALT) concentration:

Part 1: ALT >60 U/L for males, >38 U/L for females, and ≤10 X ULN.

Part 2: ALT ≤ULN

Amended text:

Alanine aminotransferase (ALT) concentration:

Part 1: **ALT < 5 X ULN** ~~ALT >60 U/L for males, >38 U/L for females, and ≤10 X ULN~~.

Part 2: ALT ≤ULN

Section 5.4.1, Liver Chemistry Stopping Criteria, Paragraph 3

Rationale for change: Minor edit for clarity to align with the change made to inclusion criteria 9 to include subjects with normal to elevated ALT < 5 X ULN.

Original text:

Eligible subjects in Part 1 should have an elevated ALT at screening as specified in Section 5.1

Amended text:

Eligible subjects in Part 1 ~~should~~ **may** have an elevated ALT at screening as specified in Section 5.1

Section 7.1, Time and Events Tables, Table 10

Rationale for change: minor edit for clarity to re-order and re-number superscript/footnoes.

Original Table 10 and footnotes (excerpt- For review purposes, only the rows and text that have been changed are shown below):

Table 10 Time and Events Table: Day 2 to Day 60 of Single Ascending Dose (Part 1)

	Day 2	DAY 3	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 30 (±1 day)	Day 60 (±1 day)	ET
	Post Dose in Hours (h)							
Laboratory Assessments								
Pregnancy test (as appropriate)[7]			X			X	X	X
Hematology/Chemistry/Urinalysis [8,9]		X	X			X	X	X
Urine ACR[9,10]			X			X	X	X

7. Female subjects: serum hCG or urine pregnancy test.
8. Samples for clinical laboratory tests to be collected in the morning after an overnight fast of at least 8 hours.
9. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
10. Collect first morning urine void sample for ACR assessment while subjects are in study site. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.

Amended Table 10:

Table 10 Time and Events Table: Day 2 to Day 60 of Single Ascending Dose (Part 1)

	Day 2	DAY 3	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 30 (±1 day)	Day 60 (±1 day)	ET
	Post Dose in Hours (h)							
Laboratory Assessments[7]								
Pregnancy test (as appropriate)[~~7~~**8**]			X			X	X	X
Hematology/Chemistry/Urinalysis [~~8~~,9]		X	X			X	X	X
Urine ACR[9,10]			X			X	X	X

7. **Samples for clinical laboratory tests to be collected in the morning after an overnight fast of at least 8 hours** ~~Female subjects: serum hCG or urine pregnancy test~~.

8. **Female subjects: serum hCG or urine pregnancy test** ~~Samples for clinical laboratory tests to be collected in the morning after an overnight fast of at least 8 hours~~.
9. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessments.
10. Collect first morning urine void sample for ACR assessment while subjects are in study site. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.

Section 7.1, Time and Events Tables, Table 11

Rationale for change: minor edit for clarity to remove inappropriate superscript (does not apply).

Original Table 11 (excerpt- For review purposes, only the row that has been changed is shown below):

Table 11 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Weekly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11,12]				X[11,12]				X[11,12]				

Amended Table 11:

Table 11 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Weekly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11,~~12~~]				X[11,~~12~~]				X[11,~~12~~]				

Section 7.1, Time and Events Tables, Table 13

Rationale for change: minor edit for clarity to remove inappropriate superscript (does not apply).

Original Table 13 (excerpt- For review purposes, only the row that has been changed is shown below):

Table 13 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Bi-Weekly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11,12]				X[11,12]				X[11,12]				

Amended Table 13:

Table 13 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Bi-Weekly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11,~~12~~]				X[11,~~12~~]				X[11,~~12~~]				

Section 7.1, Time and Events Tables, Table 15

Rationale for change: minor edit for clarity to remove inappropriate superscript (does not apply).

Original Table 15 (excerpt- For review purposes, only the row that has been changed is shown below):

Table 15 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Monthly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11, 12]				X[11,12]				X[11, 12]				

Amended Table 15:

Table 15 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Monthly Dosing

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)
PK sampling[11]	X[11,~~12~~]				X[11,~~12~~]				X[11,~~12~~]				

12.7.3. Protocol changes for Amendment 03 (28-JUNE-2017) from Protocol Amendment 02 (07-MAR-2017)

Protocol Amendment 3 replaces the protocol amendment 2 dated 07 Mar 2017 and applies to all study sites.

Protocol Amendment 3 is being implemented for the following reasons:

- To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.
    - Rationale: The purpose of the single dose administration in Part 1 is to examine target engagement (e.g., effect on viral biomarkers) and safety of GSK3389404 in HBV patients. Safety data is already available from the first-in-human healthy volunteer study (202007), with no reported deaths or SAEs following single and multiple dose administration. Based on investigator feedback and internal discussion it was determined that the effect on viral biomarkers should be evident within a cohort of 3 active, 1 placebo. Study 205670 is not statistically powered and reducing the sample size of Part 1 will not affect the scientific integrity of the program.

- To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.
    - Rationale: The primary viral efficacy marker is the reduction of HBsAg and this reduction can be evaluated equally well in HBeAg positive, HBeAg negative and in patients receiving nucleos(t)ide therapy. Based on investigator feedback, the sponsor would like to widen the entry criteria to i) include patients currently on stable nucleos(t)ide therapy and ii) allow both HBeAg negative and positive patients into cohorts A, B, C and D rather than restricting recruitment to HBeAg positive patients.
- To remove the requirement for a minimum viral load at entry for treatment naïve subjects or subjects that have had prior treatment with interferon or nucleosides in Part 1.
    - Rationale: The primary efficacy endpoint is reduction in HBsAg and as such restricting the population to a minimum HBV DNA threshold is an unnecessary restriction.
- To update the subject population in Parts 1 and 2 to include women of child bearing potential
    - Rationale: The risk of GSK3389404 to women of child bearing potential is considered to be low based upon pre-clinical embryo-fetal development studies to date with the GSK3389404 compound and with the ASO class in general. Appropriate pregnancy precautions (e.g., double barrier contraceptives) will be implemented and pregnancy testing will be conducted before (serum at screening, urine prior to dosing) and during the study.

- To update the subject population in Parts 1 and 2 to include patients with GFR ≥60 mL/min after consultation with the GSK medical monitor.
    - Rationale: In young adults, although the normal GFR number is >90 mL/min, many older subjects will have GFR below 90 mL/min in the absence of kidney disease. Consequently, the sponsor has revised the protocol to allow patients with a GFR number of ≥60 mL/min to participate in the study if after consultation with the GSK medical monitor the patient does not have a history or active diagnosis of renal disease.
- To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.
    - Rationale: Japan may also participate in an optional Japanese Part 2 sub-study. The protocol amendment 3 is updated to reflect the potential increase in number of subjects who may be exposed to GSK3389404.
- To reduce complexity and visit burden for subjects.
    - Rationale: Feedback from investigators suggests that the visit schedule in Parts 1 and 2 remain burdensome for subjects. In particular, it was requested to remove mandatory fasting for all visits as this does not affect safety lab parameters (except fasting glucose measurement), to remove holter monitoring (supported by the absence of pre-clinical cardiac signals and absence of findings in the first-in-human study 202007), to reduce routine ECG readings from duplicate or triplicate to single assessments and to streamline/simplify visit schedules.
- To provide information from the results of the GSK3389404 first-in-human Study 202007.
    - Rationale: The first-in-human study 202007 was recently completed and at the time of this protocol writing, the study report is being finalized. Preliminary information from study 202007 to support changes in the study design, dose selection, benefit:risk, and Time and Events assessments were included.
- To provide corrections to the statistical simulations
    - Rationale: The statistical assumptions were found to have an unintended bias, the simulations and decision criteria were updated appropriately
- To provide minor edits for clarity and typographical errors.

LIST OF CHANGES

Title Page, Authors

- Rationale: To update authors

Original Text:

Author (s): PPD

Amended Text:

Author (s): PPD [redacted]

Protocol Synopsis and Section 2.1, Study Rationale Last 2 Sentences

- Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.

Original Text:

Finally, this study will provide an initial evaluation of any differences in PD between hepatitis B virus (HBV) e antigen (HBeAg)-positive and HBeAg-negative subjects with CHB. Data from this study will support subsequent studies by providing an early assessment of safety and PD in the target patient population when GSK3389404 is administered as monotherapy (Part 1) or adjunctive therapy (Part 2).

Amended Text:

Finally, this study ~~will~~ **may** provide an initial evaluation of any differences in PD between hepatitis B virus (HBV) e antigen (HBeAg)-positive and HBeAg-negative subjects with CHB. Data from this study will support subsequent studies by providing an early assessment of safety and PD in the target patient population ~~when GSK3389404 is administered as monotherapy (Part 1) or adjunctive therapy (Part 2)~~.

Protocol Synopsis and Section 3, Objective(s) and Endpoint(s), Primary

- Rationale: To make edits for typographical error

Original text

To identify one or more efficacious dose(s) and dosing regimen(s) of GSK3389404 over a planned duration of 3 months (Part 2).	**Efficacy** Response rate (RR) based on the proportion of subjects with at least a 1.5 times log 10 copies/mL reduction of hepatitis B surface antigen (HBsAg) levels from baseline anytime during the study.

Amended text

To identify one or more efficacious dose(s) and dosing regimen(s) of GSK3389404 over a planned duration of 3 months (Part 2).	**Efficacy** Response rate (RR) based on the proportion of subjects with at least a 1.5 times log 10 ~~copies~~**IU**/mL reduction of hepatitis B surface antigen (HBsAg) levels from baseline anytime during the study.

Protocol Synopsis and Section 3, Objective(s) and Endpoint(s), Secondary

- Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.; subjects who are receiving nucleos(t)ide therapy would have suppressed HBV DNA levels

Original Text:

Secondary	
To assess the PD effect of GSK3389404 in subjects with CHB (Part 1 and Part 2).	Correlation between GSK3389404 PK parameters and PD parameters, including hepatitis B virus (HBV) deoxyribonucleic acid (DNA), HBsAg, and HBeAg levels (as appropriate, HBeAg-positive subjects).

Amended Text:

Secondary	
To assess the PD effect of GSK3389404 in subjects with CHB (Part 1 and Part 2).	Correlation between GSK3389404 PK parameters and PD parameters, including hepatitis B virus (HBV) deoxyribonucleic acid (DNA) **as appropriate**, HBsAg, and HBeAg levels (as appropriate, HBeAg-positive subjects).

Protocol Synopsis and Section 3, Objective(s) and Endpoint(s), Exploratory

- Rationale: To provide edits for clarity; to provide details regarding other PD parameters that may be assessed

Original Text:

Exploratory	
To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (Part 1 and Part 2, if applicable).	Correlation between PD parameters, including HBV DNA and HBsAg.

Amended Text:

Exploratory	
To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (Part 1 and Part 2, if applicable).	Correlation between PD parameters, including HBV DNA**, HBV RNA,** ~~and~~ HBsAg**, and/or hepatitis B core-related antigen (HBcrAg)**.

Protocol Synopsis, Overall Design, Paragraph 2, Bullets 1 through 5 and Paragraph 3

- Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.

Original Text:

Part 1 will be conducted as a single ascending dose (SAD) study with 5 planned cohorts.

- Cohort A (HBeAg-positive subjects): GSK3389404 30 mg SC or placebo
- Cohort B (HBeAg-positive subjects): GSK3389404 60 mg SC or placebo
- Cohort C (HBeAg-positive subjects): GSK3389404 120 mg SC or placebo
- Cohort C1, optional (HBeAg-negative subjects): GSK3389404 120 mg SC or placebo
- Cohort D (HBeAg-positive subjects): GSK3389404 ≤240 mg SC or placebo

Within each cohort, subjects will be randomized to receive GSK3389404 or placebo SC in a 3:1 ratio. Cohorts A, B, C, C1, and D will be conducted in a sequential fashion; Cohort C1 may be dosed after Cohort C or in parallel with Cohort D. Dose Escalation Committee meetings will be held between sequential cohorts.

Amended Text:

Part 1 plans to enroll subjects primarily from the Asia-Pacific region (including, but not limited to: Hong Kong, South Korea, and Taiwan). Part 1 will be conducted as a single ascending dose (SAD) study with **up to** 5 planned cohorts.

- Cohort A (HBeAg-positive **and/or HBeAg –negative** subjects): GSK3389404 30 mg SC or placebo
- Cohort B (HBeAg-positive **and/or HBeAg –negative** subjects): GSK3389404 60 mg SC or placebo

- Cohort C (HBeAg-positive **and/or HBeAg –negative** subjects): GSK3389404 120 mg SC or placebo
- Cohort C1**, optional** (**HBeAg-positive or** HBeAg-negative subjects): GSK3389404 120 mg SC or placebo
- Cohort D (HBeAg-positive **and/or HBeAg –negative** subjects): GSK3389404 ≤240 mg SC or placebo

Within each cohort, subjects will be randomized to receive GSK3389404 or placebo SC in a 3:1 ratio. Cohorts A, B, C, C1, and D will be conducted in a sequential fashion**.**~~,~~ Cohort C1 **is an optional cohort that** may be dosed after Cohort C or in parallel with Cohort D**.** Dose Escalation Committee meetings will be held between sequential cohorts. **The decision to enroll the optional Cohort C1 will be made at a prior Dose Escalation Committee Meeting.**

Protocol Synopsis, Overall Design, Paragraph 4, Inserted New Sentence 2 and 3

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Not applicable

Amended Text:

Part 2 plans to enroll subjects primarily from the Asia-Pacific region. Japan may also participate in an optional Japanese Part 2 sub study.

Protocol Synopsis, Overall Design, New added at Paragraph 6

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Since this is the first administration of GSK3389404 in subjects with CHB, the study design may change based on emerging data (safety, tolerability, and PD) from each cohort and/or part.

Amended Text:

Details of the optional Japanese Part 2 sub-study will be detailed in a Japan country-specific amendment/supplement.

Since this is the first administration of GSK3389404 in subjects with CHB, the study design may change based on emerging data (safety, tolerability, and PD) from each cohort and/or part.

Protocol Synopsis and Section 4.3, Type and Number of Subjects, Paragraph 1, Sentences 1 and 2

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive, and not currently receiving CHB treatment (Part 1) or currently on a stable nucleos(t)ide regimen (Part 2) are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive subjects, and Part 1 (Cohort C1) will enroll HBeAg-negative subjects.

Amended Text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive, ~~and not currently receiving CHB treatment (Part 1) or currently on a stable nucleos(t)ide regimen (Part 2)~~ are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive **and/or HBeAg-negative** subjects, and Part 1 (**optional** Cohort C1) ~~will~~ **may** enroll **HBeAg-positive or** HBeAg-negative subjects **(or none at all)**.

Protocol Synopsis and Section 4.3, Type and Number of Subjects, Paragraph 2, Sentence 1, Bullet 1 and new Bullet 3

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study

Original Text:

Approximately 120 subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo) in Part 1 and Part 2.

- In Part 1, approximately 40 subjects with CHB are planned for randomization (30 GSK3389404 and 10 placebo).
- In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment.

Amended Text:

Approximately **150** subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). **This number assumes full enrolment in the optional Japanese sub-study.**

- In Part 1, approximately ~~40~~**20 to 40** subjects with CHB are planned for randomization (30 GSK3389404 and 10 placebo **under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3**). **A range is provided because different countries and sites may be enrolling under the older versions of the protocol.**
- **If Japan participates in the optional Japanese Part 2 sub-study, approximately 22 subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement.**

Protocol Synopsys, Analysis, Part 2 and Section 9.1, Hypotheses and 9.4.1, Efficacy

- Rationale: To provide corrections to the statistical simulations

Original Text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 80%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥80%, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

Amendend Text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least **95**~~80~~%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥**95**~~80~~%, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

Protocol Synopsis, Analysis

- Rationale: To make edits for typographical error

Original text

The primary efficacy objective is to select the efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint, response rate (RR), based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least a 1.5 times log 10 copies/mL reduction of HBsAg levels from baseline anytime during the study.

Amended text

The primary efficacy objective is to select the efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint, response rate (RR), based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least a 1.5 times log 10 ~~copies~~ **IU**/mL reduction of HBsAg levels from baseline anytime during the study.

Section 2, Introduction, Last paragraph, 1st and 2nd Sentences

- Rationale: To provide minor edits for clarity

Original Text:

ISIS 505358 has been studied in healthy volunteers at various dose levels and for durations up to 1 month. GSK3389404 has been administered to healthy volunteers in Study 202007, an on-going study to assess the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses of GSK3389404. Results from the completed study of ISIS 505358 and from the single ascending dose (SAD) portion of the ongoing Study 202007 have not identified any safety findings to date that would preclude further clinical development.

Amended Text:

ISIS 505358 has been studied in healthy volunteers at various dose levels and for durations up to 1 month. GSK3389404 has been administered to healthy volunteers in Study 202007, **a recently completed** study to assess the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses of GSK3389404. Results from the completed study of ISIS 505358 and from the single ascending dose (SAD) portion of Study 202007 have not identified any safety findings to date that would preclude further clinical development.

Section 2.1 Study Rationale, Paragraph 1, Sentence 4

- Rationale: To provide minor edits for clarity

Original Text:

Finally, this study will provide an initial evaluation of any differences in PD between HBV e-antigen (HBeAg)-positive and HBeAg-negative subjects with CHB.

Amended Text:

Finally, this study **may** provide an initial evaluation of any differences in PD between HBV e-antigen (HBeAg)-positive and HBeAg-negative subjects with CHB.

Section 4.1, Overall Design, Paragraph 2, New Sentence 1

- Rationale: To provide minor edits for clarity

Original Text:

Not applicable

Part 1 plans to enroll subjects primarily from the Asia-Pacific region (including, but not limited to, Hong Kong, South Korea, and Taiwan).

Section 4.1, Overall Design, Paragraph 2, Sentence 3 and New Sentence 4

- Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.

Original Text:

Cohorts A, B, C, C1, and D will be conducted in a sequential fashion; Cohort C1 may be dosed after Cohort C or in parallel with Cohort D.

Amended Text:

Cohorts A, B, C, C1, and D will be conducted in a sequential fashion~~;~~ Cohort C1 **is an optional cohort that** may be dosed after Cohort C or in parallel with Cohort D. **The decision to enroll the optional Cohort C1 will be made at a prior Dose Escalation Committee Meeting.**

Section 4.1, Overall Design, Paragraph 2, Sentence 4

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1

Original Text:

Dosing in each cohort is contingent on the safety, PK, and PD profiles of at least 4 subjects who received GSK3389404 at the previous dose level.

Amended Text:

Dosing in each cohort is contingent on the safety, PK, and PD profiles of at least 4**3** subjects who received GSK3389404 at the previous dose level.

Section 4.1, Overall Design, Paragraph 2, New Sentence 7

- Rationale: To provide edits for clarity

Original Text:

Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Section 6.3 provides additional information on planned dose adjustments.

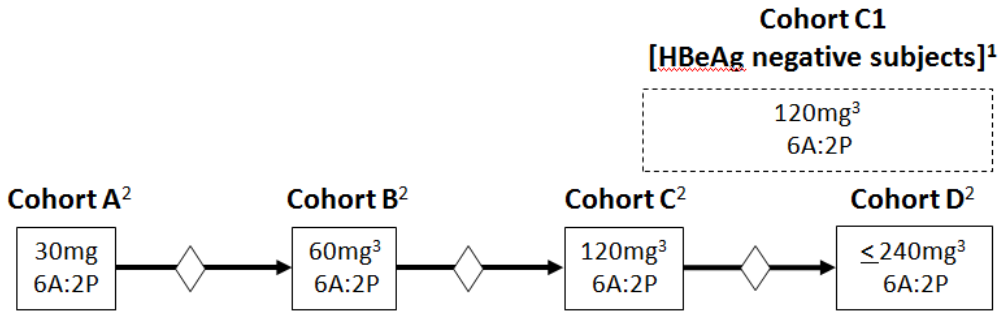
Amended Text:

Cohorts may be expanded (additional subjects may be enrolled) to further evaluate safety, PK, and/or PD findings at a given dose level. Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Section 6.3 provides additional information on planned dose adjustments.

Section 4.1, Overall Design, Figure 1

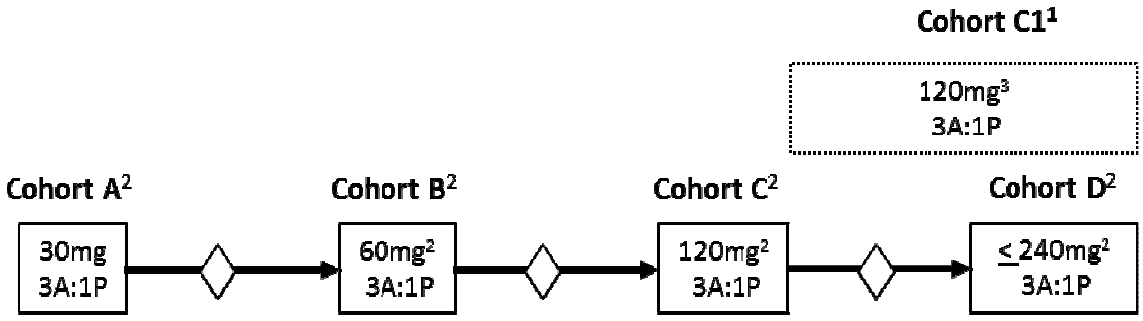
- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1; To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D.

Original Text:



A = active (GSK3389404); HBeAg = hepatitis B virus e-antigen; P = placebo.
◊ = Dose EscalationCommittee meeting
1. Cohort C1 may be dosed after Cohort C or in parallel with Cohort D.
2. HBeAg-positive subjects will be enrolled in these cohorts.
3. Dose escalations and/or reductions will progress with modifications based on the actual human safety and PK data from the preceding cohort(s). Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Dose will not exceed 240 mg.

Amended Text:



A = active (GSK3389404); HBeAg = hepatitis B virus e-antigen; P = placebo.
◊ = Dose EscalationCommittee meeting

1. Cohort C1 **may include HBeAg-positive or HBeAg-negative subjects and, if enrolled,** may be dosed after Cohort C**,** ~~or~~ in parallel with Cohort D **(optional)**.
2. HBeAg-positive **and/or HBeAg-negative** subjects will be enrolled in these cohorts.
3. Dose escalations and/or reductions will progress with modifications based on the actual human safety and PK data from the preceding cohort(s). Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD. Dose will not exceed 240 mg.

Section 4.1, Overall Design, Paragraph 4, New Sentences 2 and 3

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Not Applicable

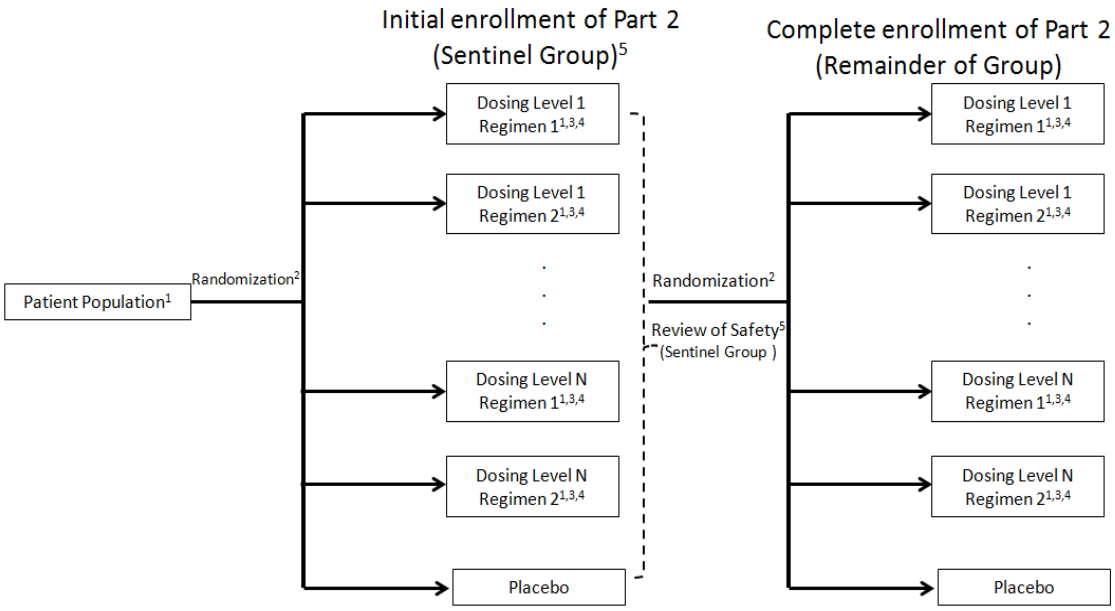
Amended Text:

Part 2 plans to enroll subjects primarily the Asia-Pacific region, including Japan. Japan may also participate in an optional Japanese Part 2 sub-study.

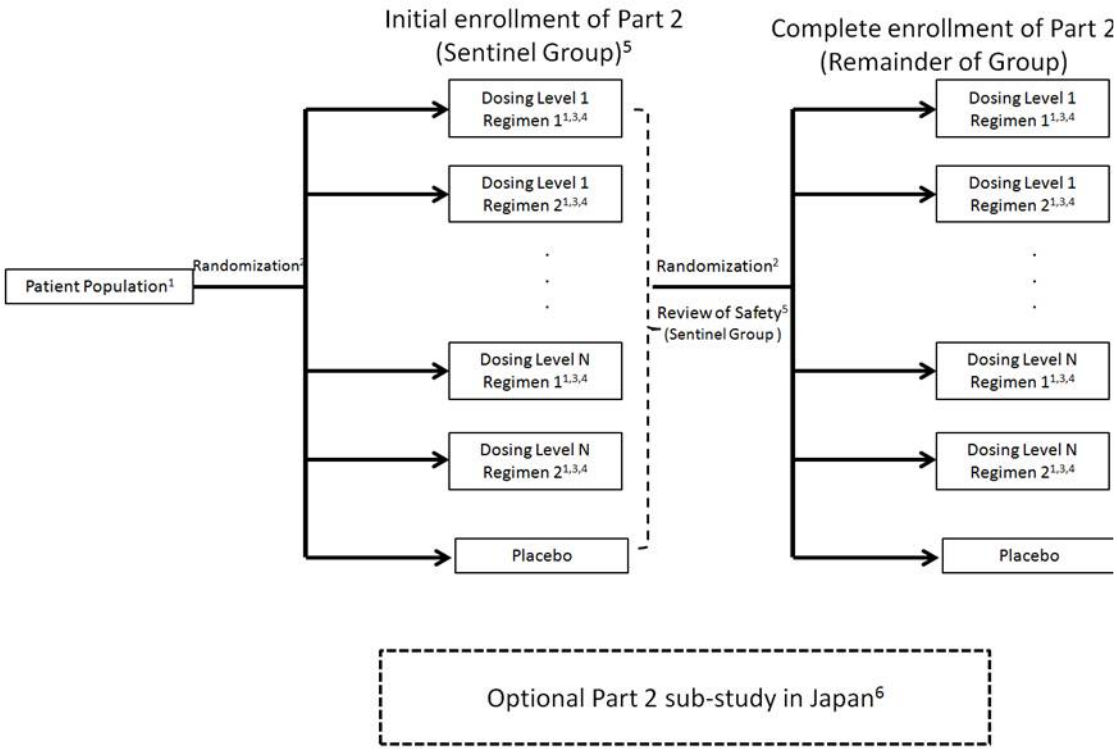
Section 4.1, Overall Design, Figure 2

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:



Amended Text:



Section 4.1, Overall Design, Figure 2, New Footnote 6

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Not applicable

Amended Text:

6. An optional Japanese Part 2 sub-study is planned. The exact details may be found in a country-specific protocol amendment/supplement and will not be detailed here. The optional Japanese Part 2 sub-study may include more intensive PK monitoring and/or potential overnight/hospital stay.

Section 4.3, Type and Number of Subjects, Paragraph 2, Bullet 2, Last Sentence and Bullet 3, First Sentence

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Enrolling approximately 80 subjects will allow for an approximate 14% overall drop-out rate, so that there are 10 evaluable subjects in each active treatment group and 12 subjects in placebo.

Amended Text:

Enrolling approximately 80 subjects will ~~allow~~ **ensure enough power for Part 2 with or without the optional Japanese Part 2 sub-study and allow** for an approximate 14% overall drop-out rate, so that there are 10 evaluable subjects in each active treatment group and 12 subjects in placebo **without the optional Japanese Part 2 sub-study for the primary analysis**.

If Japan participates in the optional Japanese Part 2 sub-study, approximately 22 subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement.

Section 4.4, Design Justification, Paragraph 2, Sentence 2

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

The sequential nature of Part 1 ensures that a range of single doses are investigated first in HBeAg-positive subjects (Part 1, Cohorts A, B, C) and HBeAg-negative subjects (Cohort C1) before exposing HBeAg-positive subjects to the highest planned dose (Cohort D).

Amended Text:

The sequential nature of Part 1 ensures that a range of single doses are investigated ~~first in HBeAg-positive subjects (Part 1, Cohorts A, B, C) and HBeAg-negative subjects (Cohort C1)~~ before exposing ~~HBeAg-positive~~ subjects to the highest planned dose (Cohort D).

Section 4.4, Design Justification, Paragraph 3, Sentences 2 and 4

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007 and clarify dose escalation

Original Text:

This starting dose is based on the review of data from the SAD portion of the ongoing clinical trial (Study 202007).
Part 2 will be initiated after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and investigator at the Dose Escalation Committee meetings for Part 1.

Part 2 will be initiated after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and investigator at the Dose Escalation Committee meetings for Part 1.

Amended Text:

This starting dose is based on the review of data from the SAD portion of the ~~ongoing~~ **recently completed** clinical trial (Study 202007**; at the time of this protocol writing, the final study report is in progress**).

Part 2 will be initiated after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the **GSK** study team and **principal** investigator (or **appropriate designee)** at the Dose Escalation Committee meetings for Part 1.
.

Section 4.5.1, Observed Human Pharmacokinetics, Paragraph 1, Sentence 3, 4 and 6

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

At the time of this protocol writing, the SAD part of Study 202007 has been completed, and the multiple ascending dose part is ongoing. The preliminary human PK parameters are presented in Table 1. Based on preliminary PK data, GSK3389404 showed dose-proportional PK with a mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose. The preliminary observed human PK data were evaluated using non-compartmental analysis (NCA) in Phoenix WinNonlin version 6.3. All ISIS50538 (GSK3228836) plasma concentrations were non-quantifiable.

Amended Text:

At the time of this protocol **amendment** writing, ~~the SAD part of~~ Study 202007 has been completed, and ~~the multiple ascending dose part is ongoing~~ **final study report is in progress**. The ~~preliminary~~ human PK parameters are presented in Table 1. Based on ~~preliminary~~ PK data, GSK3389404 showed dose-proportional PK with a mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose. The ~~preliminary~~ observed human PK data were evaluated using non-compartmental analysis (NCA) in Phoenix WinNonlin version 6.3. All ISIS50538 (GSK3228836) plasma concentrations were non-quantifiable.

Table 1, Title

Rationale: To provide clarity that results reported are not preliminary

Original Text:

Summary of Selected Preliminary Plasma GSK3389404 Pharmacokinetic Parameters in Humans

Amended Text:

Summary of Selected ~~Preliminary~~ Plasma GSK3389404 Pharmacokinetic Parameters in Humans

.

Section 4.5.5 GSK3389404 and Nucleos(t)ides 4th Paragraph, Last Sentence

Rationale: To provide clarity

Original Text:

Therefore, although GSK3389404 was shown to be extensively distributed into the kidney [Shemesh, 2016], GSK3389404 is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

Amended text:

Therefore, ~~although~~ GSK3389404 **or the primary tissue metabolite ISIS 505358 that** was shown to be extensively distributed into the kidney **in non-clinical studies**, ~~GSK3389404~~ is unlikely to interact with tenofovir, entecavir, lamivudine, adefovir and telbivudine.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Liver Effects, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In the GSK 3389404 Phase 1 study in healthy subjects (Study 202007), in Part 1 single dose, two subjects experienced mild or moderate adverse events associated with elevations in ALT. **Both were transient, modest (DAIDs criteria Grade 1 (<2.5x**

ULN))and not associated with concurrent symptoms or increases in bilirubin. In Part 2 multiple dose, no liver-chemistry related AEs were reported.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Coagulation Effects, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, there was no evidence of GSK3389404 related prolongation of aPPT.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Compliment Activation, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, no effect of GSK3389404 administration on complement (C3, C4, C5a or Bb) was observed.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Pro-inflammatory Effects/Constitutional or Flu-Like Symptoms, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, influenza-like/constitutional symptoms such as fever, chills and arthralgias were not observed. Injection site reactions were the most commonly reported treatment-related adverse

event. These AEs were mild in intensity, transient in nature and not related to dose or duration of treatment.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Kidney Effects, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, no changes in the mean values from baseline were observed.

Section 4.6.1, Risk Assessment, Table 4, Column 2 (Impact- Eligibility Criteria), Kidney Effects

- Rationale: To update the subject population in Parts 1 and 2 to include patients with GFR ≥60 mL/min after consultation with the GSK medical monitor.

Original: Subjects with serum creatinine ≥ ULN, glomerular filtration rate (GFR) < 90 mL/min

Amended text: Subjects with serum creatinine ≥ULN, glomerular filtration rate (GFR) < 90 mL/min **(but ≥60 mL/min may be considered after consultation with the GSK Medical Monitor)**

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Compelment Activation

Rationale: To provide minor edits due to typographical error

Original Text:

Complement Activation: In the monkey GSK3389404 13-week study, minimal decreases in (up to 21% from baseline) C3 and increased complement fragment Bb (up to 2.6-fold over baseline) were observed in the 8 and 30 mg/kg groups, suggesting mild activation of the alternative complement pathway.

Amended Text:

Complement Activation: In the monkey GSK3389404 13-week study, minimal decreases in (up to 21% from baseline) C3 and increased complement fragment Bb (up to **3**~~2~~.6-fold over baseline) were observed in the 8 and 30 mg/kg groups, suggesting mild activation of the alternative complement pathway.

Section 4.6.1, Risk Assessment, Table 4, Column 1 (Potential Risk/Summary of Data), Decreased hematological parameters, New Paragraph

- Rationale: To provide information from the results of the GSK3389404 first-in-human Study 202007.

Original Text:

Not applicable

Amended Text:

In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, the laboratory data did not suggest any GSK3389404 related effect on hematological cell counts or hemoglobin.

Section 4.6.2, Benefit Risk Summary, Paragraph 3, Item 4,

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

4. Between each dosing cohort in Part 1, escalation to the next dose-level will proceed only after the safety (AE listings, flagged vital signs, flagged findings during cardiac monitoring [Holter], ECGs, laboratory findings (including liver function tests) of the previous dose level, and PK results derived from 24-hour plasma profiles, together with available PD data (HBsAg levels and HBV DNA) are thoroughly reviewed by the study team and the investigator at scheduled Dose Escalation Committee meetings (Section 10.8.1).

Amended Text:

4. Between each dosing cohort in Part 1, escalation to the next dose-level will proceed only after the safety (AE listings, flagged vital signs, ~~flagged findings during cardiac monitoring [Holter],~~ ECGs, laboratory findings ~~(~~**[**including liver function tests**]**) of the previous dose level, and PK results derived from 24-hour plasma profiles, together with available PD data ~~(HBsAg levels and HBV DNA)~~ are thoroughly reviewed by the study team and the investigator at scheduled Dose Escalation Committee meetings (Section 10.8.1).

Section 5, Selection of Study Population and Withdrawal Criteria, Paragraph 1, Sentence 1, Sentence 5 and Last Sentence

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

This first-in-patient study will enroll adult male and female subjects in either the immune tolerant or the immune active phase of HBV infection who are not currently receiving HBV treatment (Part 1) or who are currently on a stable nucleos(t)ide regimen (Part 2).

The entry criteria for this study are designed to enroll subjects with CHB who do not have advanced liver fibrosis or cirrhosis, other concomitant liver diseases, co-infection, or other significant co-morbidities that would confound the safety monitoring and/or potentially put them at greater risk for treatment-related AEs.

The ALT eligibility criteria are generally consistent with the International Liver Society guidelines (e.g., Asian Pacific Association for the Study of the Liver [Liaw, 2012], European Association for the Study of the Liver [EASL, 2012], American Association for the Study of Liver Diseases [Terrault, 2016]).

Amended Text:

This first-in-patient study will enroll adult male and female subjects in either the immune tolerant or the immune active phase of HBV infection who **may or may** ~~are~~ not **be** ~~currently receiving HBV treatment (Part 1) or who are currently~~ on a stable nucleos(t)ide regimen ~~(Part 2)~~.

The entry criteria for this study are designed to enroll subjects with CHB who do not have advanced liver fibrosis or cirrhosis, other **advanced** concomitant liver diseases, co-infection, or other significant co-morbidities that would confound the safety monitoring and/or potentially put them at greater risk for treatment-related AEs.~~The ALT eligibility criteria are generally consistent with the International Liver Society guidelines (e.g., Asian Pacific Association for the Study of the Liver [Liaw, 2012], European Association for the Study of the Liver [EASL, 2012], American Association for the Study of Liver Diseases [Terrault, 2016]).~~

Section 5.1, Inclusion Criteria, Item 4.

- Rationale: To update the subject population in Parts 1 and 2 to include women of child bearing potential.

Original Text:

4. Male or female if they satisfy the following:

    a. Females of reproductive potential are not permitted. Eligible females must meet the following criteria:

        i. Non-pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test); AND

        ii. Non-lactating at screening and prior to dosing; AND

        iii. Non-reproductive potential as defined by at least one of the following conditions:

1. Premenopausal females without reproductive potential defined by one of the following:

a. Documented salpingectomy;

b. Hysterectomy;

c. Documented bilateral oophorectomy.

2. Postmenopausal defined as 12 months of spontaneous amenorrhea.

3. A blood sample for simultaneous follicle-stimulating hormone (FSH) and estradiol levels may be collected at the discretion of the investigator or site to confirm non-reproductive potential. Please refer to laboratory reference ranges for confirmatory levels for menopause.

b. Male subjects with a female partner of child-bearing potential must agree to meet one of the contraception requirements from the time of first dose of study treatment until the final Follow-up visit.

i. Vasectomy

ii. Male condom plus partner's use of one of the contraceptive options below that meets the standard operating procedure (SOP) effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

1. Contraceptive subdermal implant

2. Intrauterine device or intrauterine system

3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]

4. Injectable progestogen [Hatcher, 2011]

5. Contraceptive vaginal ring [Hatcher, 2011]

6. Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Amended Text:

4. Male or female if they satisfy the following:

a. **All** ~~F~~**f**emales ~~of reproductive potential are not permitted. Eligible females~~ must meet the following criteria:

i. Non-pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test); AND

ii. Non-lactating at screening and prior to dosing; AND

b. ~~iii.~~ **Females of** ~~Non-~~reproductive potential **(FRP) must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until the final Follow-up visit in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.**

c. For females of non-reproductive potential, ~~as defined by~~ at least one of the following conditions **must apply**:

~~1.~~ **i.** Premenopausal females without reproductive potential defined by one of the following:

~~a.~~ **1.** Documented salpingectomy;

~~b.~~ **2.** Hysterectomy;

~~c.~~ **3.** Documented bilateral oophorectomy.

~~2~~**ii.** Postmenopausal defined as 12 months of spontaneous amenorrhea.

~~3~~**iii**. A blood sample for simultaneous follicle-stimulating hormone (FSH) and estradiol levels may be collected at the discretion of the investigator or site to confirm non-reproductive potential. Please refer to laboratory reference ranges for confirmatory levels for menopause.

~~b~~**d**. Male subjects with a female partner of child-bearing potential must agree to meet one of the contraception requirements from the time of first dose of study treatment until the final Follow-up visit.

i. Vasectomy

ii. Male condom plus partner's use of one of the contraceptive options below that meets the standard operating procedure (SOP) effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

1. Contraceptive subdermal implant

2. Intrauterine device or intrauterine system

3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]

4. Injectable progestogen [Hatcher, 2011]

5. Contraceptive vaginal ring [Hatcher, 2011]

6. Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

e. Male subjects must refrain from donating sperm from the time of first dose of study treatment until the final Follow-up visit.

Section 5.1, Inclusion Criteria, Item 5.

Rationale: To provide clarity, documentation of chronic HBV infection is sufficient, does not require HBsAg only.

Original Text:

5. Documented chronic HBV infection, defined as positive plasma or serum HBsAg ≥6 months prior to screening.

Amended Text:

5. Documented chronic HBV infection~~, defined as positive plasma or serum HBsAg~~ ≥6 months prior to screening.

Section 5.1, Inclusion Criteria, Item 6.a.

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

6. Subject with HBV treatment history as follows:
   a. Part 1: Treatment naive or have had prior treatment with interferon (pegylated or non-pegylated) that must have ended at least 12 months prior to the Baseline visit (Day 1 pre-dose) and/or nucleos(t)ide analogue therapy that must have ended at least 6 months prior to the Baseline visit.

Amended Text:

6. Subject with HBV treatment history as follows:
   a. Part 1:

i. Treatment naïve, -or-

ii. **H**~~h~~ave had prior treatment with interferon (pegylated or non-pegylated)) that must have ended at least ~~12~~**6** months prior to the Baseline visit (Day 1 pre-dose) and/or nucleos(t)ide analogue therapy that must have ended at least 6 months prior to the Baseline visit~~.~~**, –or-**

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

Section 5.1, Inclusion Criteria, Item 7.

- Rationale: To remove the requirement for a minimum viral load at entry for treatment naïve subjects or subjects that have had prior treatment with interferon or nucleosides in Part 1.

Original Text:

7. Plasma or serum HBV DNA concentration:
   a. Part 1:
      i. ≥20,000 IU/mL for HBeAg-positive subject
      ii. ≥2000 IU/mL for HBeAg-negative subjects
   b. Part 2: HBV DNA must be adequately suppressed, defined as plasma or serum HBV DNA <LLOQ.

Amended Text:

7. Plasma or serum HBV DNA concentration:
   a. Treatment naïve subjects or subjects not currently receiving treatment, there is no minimum HBV DNA requirement.
   b. Subjects who are receiving stable nucleos(t)ide analogue therapy must be adequately suppressed, defined as plasma or serum HBV DNA <LLOQ.

Section 5.1, Inclusion Criteria, Item 9.

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

9. Alanine aminotransferase (ALT) concentration:
   a. Part 1: ALT < 5 X ULN

b. Part 2: ALT ≤ULN

Amended Text:

9. Alanine aminotransferase (ALT) concentration:

~~a. Part 1:~~

a. ALT < 5 X ULN **for treatment naïve subjects and for subjects who are not currently receiving treatment**

b. **ALT ≤ULN for subjects who are receiving stable nucleos(t)ide analogue therapy**

Section 5.2, Exclusion Criteria, Item 1.a.

- Rationale: To provide minor edits for clarity

Original Text:

1. Medical history

a. History of or active diagnosis of liver disease other than CHB, such as autoimmune hepatitis, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, hemochromatosis, or liver failure.

b. History or other clinical evidence of hypertension significant or unstable cardiac disease (e.g., prolonged QT syndrome [torsade de pointes], angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease and/or clinically significant ECG abnormalities).

Amended Text:

1. Medical history

a. History of or active diagnosis of **moderate to severe** liver disease other than CHB, such as autoimmune hepatitis, ~~non-alcoholic fatty liver disease/~~non-alcoholic steatohepatitis, hemochromatosis, or liver failure.

b. History or other clinical evidence of ~~hypertension~~ significant or unstable cardiac disease (e.g., prolonged QT syndrome [torsade de pointes], angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease and/or clinically significant ECG abnormalities).

Section 5.2, Exclusion Criteria, Items 5, 6, 7

Rationale: To provide minor edits for clarity

Original Text:

5. A positive hepatitis C virus (HCV) antibody test
6. A positive human immunodeficiency virus (HIV) antibody test
7. Positive hepatitis D virus (HDV) antibody test

Amended Text:

5. ~~A positive h~~**H**epatitis C virus (HCV) ~~antibody test~~ **co-infection**
6. ~~A positive h~~**H**uman immunodeficiency virus (HIV) ~~antibody test~~ **co-infection**
7. ~~Positive h~~**H**epatitis D virus (HDV) ~~antibody test~~ **co-infection**

Section 5.2, Exclusion Criteria, Item 8.f

- Rationale: To update the subject population in Parts 1 and 2 to include patients with GFR ≥60 mL/min after consultation with the GSK medical monitor.

Original Text:

f. Glomerular filtration rate (GFR) <90 mL/min as calculated by the Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) formula.

   Subjects with GFR <90 mL/min but ≥80 mL/min may be considered after consultation with the GSK medical monitor.

Amended Text:

f. Glomerular filtration rate (GFR) <90 mL/min as calculated by the Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) formula.

   Subjects with GFR <90 mL/min but ≥~~80~~**60** mL/min may be considered after consultation with the GSK medical monitor.

Section 5.2, Exclusion Criteria, Item 16

- Rationale: To provide edits for clarity

Original Text:

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

Amended Text:

16. Prior treatment with any **non-GSK** oligonucleotide or small interfering RNA (siRNA) within 12 months prior to the first dosing day **or prior treatment with GSK oligonucleotide within 3 months prior to the first dosing day**.

Section 5.2, Exclusion Criteria, Item 17

- Rationale: To provide edits for clarity

Original Text:

Not Applicable

Amended Text:

Pregnant or lactating females at screening and prior to dosing

Section 5.4, QTc and Hematological Stopping Criteria

- Rationale: To provide minor edits for clarity. Changes in this section were made to clarify that subjects were not to be withdrawn from the study, rather the intent was to withdraw subjects from study treatment or to discontinue study treatment and continue with safety follow up procedures and visits. Excerpts are shown below.

Original Text:

QTc Stopping Criteria:

A subject who meets either of the bulleted criteria below will be withdrawn from the study.

Withdrawal of subjects will be based on average QTcF from triplicate ECGs.

Hematological Stopping Criteria:

In Parts 1 and 2, a subject who meets any of the criteria below will be withdrawn from study treatment

Amended Text:

QTc Stopping Criteria:

A subject who meets either of the bulleted criteria below will be ~~withdrawn~~ **discontinued** from the study **treatment**

~~Withdrawal~~ **Discontinuation** of subjects will be based on average QTcF from triplicate ECGs.

Hematological Stopping Criteria:

In Parts 1 and 2, a subject who meets any of the criteria below will be **discontinued**~~withdrawn~~ from study treatment

Section 5.4.4, Renal Function Stopping Criteria, Sentence 1

- Rationale: To provide minor edits for clarity

Original Text:

If the following are observed in Part 1 or Part 2, results should be confirmed**,** and if confirmed, further evaluation for alternative causes should be pursued in consultation with the medical monitor:

Amended Text:

If **any of** the following are observed in Part 1 or Part 2, results should be confirmed**,** and if confirmed, further evaluation for alternative causes should be pursued in consultation with the medical monitor:

Section 6.1, Investigational Produce and Other Study Treatment, Paragraph 2, Sentence 2

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

Study treatment administration will take place in the morning after a minimum 8-hour overnight fast and after completion of all pre-dose study assessments as specified in the Time and Events Tables (Section 7.1).

Amended Text:

Study treatment administration will take place ~~in the morning after a minimum 8-hour overnight fast and~~ after completion of all pre-dose study assessments as specified in the Time and Events Tables (Section 7.1).

Section 6.2, Treatment Assignment, Paragraph 1, Sentence 2

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

In addition, for Part 2, separate randomization schedules will be generated for the sentinel subjects and the remainder of Part 2 subjects.

Amended Text:

Separate randomization schedules will be generated for each part of the study**.** ~~In addition, for Part 2, separate randomization schedules will be generated for the sentinel subjects and the remainder of Part 2 subjects.~~ **The randomization schedule for the optional Japanese Part 2 sub-study will be generated separately.**

Section 6.2, Treatment Assignment, Paragraphs 3 and 4

Rationale: To provide edits for clarity

Original Text:

Two randomization schedules for Part 2 will be generated (one for the sentinel group and one for the remainder of subjects to complete Part 2 enrollment) after Part 1 is completed

and dose levels and regimens for Part 2 have been identified. Two or 3 dose levels each at 2 different dosing regimens will be explored.

A separate randomization schedule will be generated for the sentinel group (1 subject from each active treatment group and the corresponding matching placebo). The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo.

Amended Text:

Two randomization schedules for Part 2 will be generated ~~(one for the sentinel group and one for the remainder of subjects to complete Part 2 enrollment)~~ after Part 1 is completed and dose levels and regimens for Part 2 have been identified. A separate randomization schedule will be generated for the sentinel group**. The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo**. Two or 3 dose levels each at 2 different dosing regimens will be explored.

~~A separate randomization schedule will be generated for the sentinel group (1 subject from each active treatment group and the corresponding matching placebo). The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo.~~

Section 6.2, Treatment Assignment, Paragraph 5

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Subjects will be randomized in a 1:1 ratio (active:placebo) in the sentinel group. Remainder of the Part 2 subjects will be randomized in an approximately 10:1 ratio (active:placebo). The overall randomization ratio of Part 2 will be an approximately 11:2 ratio (active:placebo).

Amended Text:

Subjects **in Part 2** will be randomized in a 1:1 ratio (active:placebo) in the sentinel group. Remainder of the Part 2 subjects will be randomized in an approximately 10:1 ratio (active:placebo). The overall randomization ratio of Part 2 will be an approximately 11:2 ratio (active:placebo). **The randomization ratio of the optional Japanese Part 2 sub study will be provided in a Japan country-specific protocol amendment/supplement.**

	Sentinel		Remainder	
Part 2	**Active**	**Placebo**	**Active**	**Placebo**
Dose Level 1, Regimen 1[a]	**1**	**1**	**10**	**1**
Dose Level 1, Regimen 2[a]	**1**	**1**	**10**	**1**
Dose Level 2, Regimen 1[a]	**1**	**1**	**10**	**1**
Dose Level 2, Regimen 2[a]	**1**	**1**	**10**	**1**

Dose Level 3, Regimen 1[a]	**1**	**1**	**10**	**1**
Dose Level 3, Regimen 2[a]	**1**	**1**	**10**	**1**

a. The actual dose levels and regimens will be identified after review of data from Part 1. Up to 3 dose levels and 2 regimens will be studied.

Section 6.3, Planned Dose Adjustments, Paragraph 1, Bullet 1

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.

Original Text:

- In Part 1, the decision to proceed to the next dose level of GSK3389404, to adjust the next dose level, or add/remove cohorts will be made by the Dose Escalation Committee (Section 10.8.1) based on safety, tolerability and preliminary PK and/or PD data through Day 3 obtained in at least 4 subjects that received GSK3389404 at the prior dose level.

Amended Text:

- In Part 1, the decision to proceed to the next dose level of GSK3389404, to adjust the next dose level, or add/remove cohorts will be made by the Dose Escalation Committee (Section 10.8.1) based on safety, tolerability and preliminary PK and/or PD data through Day 3 obtained in at least **43** subjects that received GSK3389404 at the prior dose level.

Section 6.3, Planned Dose Adjustments, Paragraph 1, Bullet 1, Sub-bullet 2

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1; to provide edits for clarity

Original Text:

  - A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 465.75 µg•h/mL and 57.9 µg/mL (mean exposures at NOAEL dose in monkey at steady state), respectively, will be calculated for the next dose levels and used together with safety and tolerability data to aid next dose selection.

Amended Text:

  - A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 465.75 µg•h/mL and 57.9 µg/mL (mean exposures at NOAEL dose in monkey at steady state), respectively, ~~will~~ **may** be calculated **with adequate data** for the next dose levels and used together with safety and tolerability data to aid next dose selection.

Section 6.3, Planned Dose Adjustments, Paragraph 1, Bullet 1, Sub-bullet 4, Sentence 1

- Rationale: To provide edits for clarity

Original Text:

- The dosing plan may also be adjusted to expand a dosing cohort to further evaluate safety, PK, and/or PD findings at a given dose level, or to add a cohort to evaluate 1 additional dose level.

Amended Text:

- The dosing plan may also be adjusted to expand a dosing cohort **(enroll additional subjects)** to further evaluate safety, PK, and/or PD findings at a given dose level, or to add ~~a~~ cohort**(s)** to evaluate 1 additional dose level**(s), not exceeding the maximum dose as defined in Section 4.1**.

Section 6.10, Treatment after the End of the Study

- Rationale: To provide edits for clarity

Original Text:

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

- In Part 1, subjects with CHB may be evaluated by the investigator for initiation of standard of care therapy after the final Follow-up visit (Day 60).
- In Part 2, subjects with CHB may discuss post-study care with the investigator.

Amended Text:

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

- ~~In Part 1, subjects with CHB may be evaluated by the investigator for initiation of standard of care therapy after the final Follow-up visit (Day 60).~~
- ~~In Part 2, subjects with CHB may discuss post-study care with the investigator~~.

Section 6.11.1, Meals and Dietary Restrictions, delete Paragraph 1

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

In Part 1 and Part 2, food and drink (other than water) will be restricted for the 8 hours prior to each dose administration. Subjects should be instructed to come into the clinic fasting for all outpatient visits, except for the Screening visit.

Amended Text:

~~In Part 1 and Part 2, food and drink (other than water) will be restricted for the 8 hours prior to each dose administration. Subjects should be instructed to come into the clinic fasting for all outpatient visits, except for the Screening visit.~~

Section 6.1.11, Meals and Dietary Restrictions, Paragraph 2, Bullet 1

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

- On Day 1, a morning snack (not full meal) will be provided after dosing and completion of morning study procedures. Lunch will be provided approximately 4 hours post-dose. If subjects are still on-site, dinner will be provided approximately 9 hours post-dose and an evening snack may be available until 22:00 hours.

Amended Text:

- On Day 1, a ~~morning~~ snack (not full meal) will be provided after dosing and completion of ~~morning~~ study procedures. **A meal or l**~~L~~unch will be provided approximately 4 hours post-dose. If **appropriate** ~~subjects are still on-site~~, dinner will be provided approximately 9 hours post-dose and an evening snack may be available until 22:00 hours.

Section 6.11.1, Meals and Dietary Restrictions, Paragraph 3

- Rationale: To provide minor edits for clarity

Original Text:

During Part 2 (and Part 1 outpatient visits), subjects will be offered a meal (e.g., bagged or canteen) after completion of all study procedures at each outpatient visit.

Amended Text:

During Part 2 (and Part 1 outpatient visits), subjects will be offered a meal (e.g., bagged or canteen **[or reimbursed]**) after completion of all study procedures at each outpatient visit.

Section 6.12.1, Permitted Medications and Non-Drug Therapies, New Sentence 1

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

Not applicable

Amended Text:

In Part 1, permitted medication includes nucleos(t)ide agents such as tenofovir, entecavir, lamivudine, adefovir and telbivudine. Treatment naïve patients should

avoid initiating HBV therapy until completion of the final follow-up visit unless deemed medically necessary by the investigator.

Section 6.12.2, Permitted Medications and Non-Drug Therapies, Sentence 1 and Bullets 1 and 2

Rationale: To update the subject population in Part 1 to allow inclusion of subjects on nucleos(t)ide therapy and hepatitis B virus e-antigen (HBeAg) negative patients into Cohorts A, B, C and D. Original Text:

The following concomitant medications are not permitted during Part 1:

- Interferon (pegylated or non-pegylated) from 12 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).
- Nucleos(t)ide analogue therapy from 6 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion6, Section 5.1).

Amended Text:

~~The following concomitant medications are not permitted during Part 1:~~

- ~~Interferon (pegylated or non-pegylated) from 12 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion 6, Section 5.1).~~
- ~~Nucleos(t)ide analogue therapy from 6 months prior to Baseline (Day 1 pre-dose) through the final Follow-up visit (see Inclusion Criterion6, Section 5.1).~~

Section 6.12.2, Permitted Medications and Non-Drug Therapies, Sentence 2, Bullet 2

- Rationale: To provide minor edits for clarity

Original Text:

- Oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit (see Exclusion Criterion 16, Section 5.2).

Amended Text:

- **Non-GSK o**~~O~~ligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit **or prior treatment with a GSK oligonucleotide from 3 months prior to Day 1 through the final Follow-up visit** (see Exclusion Criterion 16, Section 5.2).

Section 7, Study Assessments and Procedures, Paragraphs 3 and 4

- Rationale: To reduce complexity and visit burden for subjects

Original Text:

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. 12-lead ECG
2. Vital signs
3. Blood collection

Assessment timing should allow the blood collection to occur at the exact nominal time.

Amended Text:

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** ~~the assessments should occur in the following order:~~

~~1. 12-lead ECG~~
~~2. Vital signs~~
3. ~~Blood collection~~

~~Assessment timing~~ should allow the blood collection to occur at the exact nominal time.

Section 7.1, Time and Events, Table 8, Footnotes 2 and 3

- Rationale: To reduce complexity and visit burden for subjects

Original Text:

2. Temperature and respiration rate (single measurement); blood pressure and heart rate (after 5 minutes of rest in the semi-supine or supine position): taken in triplicate.
3. 12-lead ECGs to be measured in triplicate after 5 minutes of rest in the semi supine or supine position.

Amended Text:

2. Temperature and respiration rate (single measurement); blood pressure and heart rate (**single measurement** after 5 minutes of rest in the semi-supine or supine position)~~: taken in triplicate~~.
3. 12-lead ECGs ~~to be measured in triplicate~~ **(single measurement** after 5 minutes of rest in the semi supine or supine position**)**.

Section 7.1, Time and Events, Table 9, Footnote 3

- Rationale: To reduce complexity and visit burden for subjects

Original Text:

3. Study treatment will be administered as subcutaneous injection(s) in the morning following an overnight fast of at least 8 hours and subsequent laboratory assessments prior to dosing.

Amended Text:

3. Study treatment will be administered as subcutaneous injection(s) ~~in the morning following an overnight fast of at least 8 hours and~~ subsequent **to** laboratory assessments prior to dosing.

Section 7.1, Time and Events, Table 9, Footnote 4

- Rationale: To reduce complexity and visit burden for subjects

Original Text:

4. On Day 1, subjects may receive a morning snack (not full meal) after completion of morning study procedures and post-dose, prior to lunch. Lunch will be approximately 4 hours (±1 hour) dosing. If subjects are still on site, dinner will be provided approximately 9 hours (±1 hour) after dosing. An evening snack (optional) may be provided until 22:00 hours.

Amended text

4. On Day 1, subjects may receive a ~~morning~~ snack (not full meal) after completion of ~~morning~~ study procedures and post-dose~~, prior to lunch~~. **A meal or l** ~~l~~Lunch will be approximately 4 hours (±1 hour) dosing. If **appropriate** ~~subjects are still on site~~, dinner will be provided approximately 9 hours (±1 hour) after dosing. An evening snack (optional) may be provided until 22:00 hours

Section 7.1, Time and Events, Table 9, Footnote 5

Rationale: To provide edits for clarity

- Original Text:

5. Adverse events will be collected from the time of informed consent and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Amended Text:

5. Adverse events will be collected from the **first dose of study treatment** ~~time of informed consent~~ and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and

SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Section 7.1, Time and Events, Table 9, Footnote 6

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

6. Temperature, respiration rate (single measurement); blood pressure and heart rate (after 5 minutes of rest in the semi supine or supine position): taken in triplicate pre-dose on Day 1 and duplicate at all other measurement time points.

Amended Text:

6. Temperature, respiration rate (single measurement); blood pressure and heart rate (**single measurement** after 5 minutes of rest in the semi supine or supine position)~~: taken in triplicate pre-dose on Day 1 and duplicate at all other measurement time points~~.

Section 7.1, Time and Events Tables, Table 9, Footnote 7

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

7. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi supine or supine position and duplicate at all other measurement time points.

Amended Text:

7. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi supine or supine position and ~~duplicate~~ **single measurements** at all other ~~measurement~~ time points.

Section 7.1, Time and Events, Table 9, Footnote 9

- Rationale: To reduce complexity and visit burden for subjects; to update the subject population in Parts 1 and 2 to include women of child bearing potential.

Original Text:

9. Female subjects at screening and pre-dose: serum hCG pregnancy test; all other time points: serum hCG or urine pregnancy test.

Amended Text:

9. Female subjects at screening ~~and pre-dose~~: serum hCG pregnancy test; all other time points: serum hCG or urine pregnancy test. **(Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)**

Section 7.1, Time and Events, Table 9, Footnote 10

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

10. Sample must be obtained after an overnight fast (at least 8 hours) and before breakfast.

Amended Text:

10. Sample must be obtained **prior to dosing** ~~after an overnight fast (at least 8 hours) and before breakfast~~.

Section 7.1, Time and Events, Table 9, Footnote 12

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

12. Collect first morning urine void sample for ACR assessment while subjects are in study site.

Amended Text:

12. Collect first morning urine void sample for ACR assessment ~~while subjects are in study site~~. **Subjects may be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their visit.**

Section 7.1, Time and Events Tables, Table 9, Row 13 and Footnote 14

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

Holter		X	X	X	X	X	X	X	X	X	

14. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

Amended Text:

~~Holter~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	

14. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb **as well as HBV RNA, HBcrAg, and/or IDO** may be analyzed from the archived ~~plasma~~ sample**s**.

Section 7.1, Time and Events Tables, Table 10, Footnote 1

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

1. On Day 2, breakfast, lunch, and dinner may be provided. If subjects choose to stay in-house through Day 3, then on Day 2, lunch will also be served approximately 4 hours (±1 hour) after the breakfast, dinner will be served approximately 9 hours (±1 hour) after the breakfast, and an evening snack (optional) may be provided until 22:00 hours. If subjects choose to stay in-house

through Day 3, they will be offered a meal (e.g., bagged or canteen) after completion of all study procedures and prior to discharge on Day 3.

Amended Text:

1. On Day 2, breakfast, lunch, and dinner may be provided. If subjects choose to stay in-house through Day 3, then on Day 2, lunch will also be served approximately 4 hours (±1 hour) after the breakfast, dinner will be served approximately 9 hours (±1 hour) after the breakfast, and an evening snack (optional) may be provided until 22:00 hours. If subjects choose to stay in-house through Day 3, they will be offered a meal (e.g., bagged or canteen **[or reimbursed]**) after completion of all study procedures and prior to discharge on Day 3.

Section 7.1, Time and Events Tables, Table 10, Footnote 3, sentence 1

Rationale: To provide clarity. Adverse events are those possibly related to study treatment and therefore cannot occur unitl after first dose of study treatment.

Original text:

Adverse events will be collected from the time of informed consent and until the final Follow-up visit.

Amended text

Adverse events will be collected from the time of ~~informed consent~~ **first dose of study treatment** and until the final Follow-up visit.

Section 7.1, Time and Events Tables, Table 10, Footnote 4

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

4. Temperature and respiration rate (single measurement); blood pressure and heart rate will be measured in duplicate after 5 minutes of rest in the semi-supine or supine position.

Amended Text:

4. Temperature and respiration rate (single measurement); blood pressure and heart rate ~~will be~~ **(single measurement** ~~in duplicate~~ after 5 minutes of rest in the semi-supine or supine position**)**.

Section 7.1, Time and Events Tables, Table 10, Footnote 5

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

5. 12 lead ECGs to be measured in duplicate after 5 minutes of rest in the semi-supine or supine position.

Amended Text:

5. **Single** 12 lead ECGs ~~to~~ **will** be measured ~~in duplicate~~ after 5 minutes of rest in the semi-supine or supine position.

Section 7.1, Time and Events Tables, Table 10, Footnote 7

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

7. Samples for clinical laboratory tests to be collected in the morning after an overnight fast of at least 8 hours.

Amended Text:

7. Samples for clinical laboratory tests to be collected **after vital sign and ECG assessments** ~~in the morning after an overnight fast of at least 8 hours~~.

Section 7.1, Time and Events Tables, Tables 11, 13, and 15

- Rationale: To reduce complexity and visit burden for subjects. To consider subjects' personal schedules and provide some flexibility in visits.

Original Text:

	Treatment Period												
Assessment	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)	Day 36 (±1 day)	Day 43 (±1 day)	Day 50 (±1 day)	Day 57 (±1 day)	Day 64 (±1 day)	Day 71 (±1 day)	Day 78 (±1 day)	Day 85 (±1 day)

Amended Text:

	Treatment Period												
Assessment	Day 1	Day 8 (±~~1~~ **2** day)	Day 15 (±~~1~~**2** day)	Day 22 (±~~1~~**2** day)	Day 29 (±~~1~~**2** day)	Day 36 (±~~1~~**2** day)	Day 43 (±~~1~~**2** day)	Day 50 (±~~1~~**2** day)	Day 57 (±~~1~~**2** day)	Day 64 (±~~1~~**2** day)	Day 71 (±~~1~~**2** day)	Day 78 (±~~1~~**2** day)	Day 85 (±~~1~~**2** day)

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 2

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

2. Study treatment will be administered as subcutaneous injection(s) in the morning following an overnight fast of at least 8 hours and subsequent to the laboratory collection and other study assessments conducted prior to dosing.

Amended Text:

2. Study treatment will be administered as subcutaneous injection(s) ~~in the morning following an overnight fast of at least 8 hours and~~ subsequent to the laboratory collection and other study assessments conducted prior to dosing.

Section 7.1, Time and Events Tables, Tables 10, 11, 13, and 15, Footnote 3

- Rationale: To provide edits for clarity

Original Text:

3. Adverse events will be collected from the time of informed consent and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Amended Text:

3. Adverse events will be collected from the **first dose of study treatment** ~~time of informed consent~~ and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 4

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

4. Temperature, respiration rate (single measurement); blood pressure and heart rate (after 5 minutes of rest in the semi-supine or supine position): taken in triplicate pre-dose on Day 1 and duplicate at all other measurement time points.

Amended Text:

4. Temperature, respiration rate (single measurement); blood pressure and heart rate (**single measurement** after 5 minutes of rest in the semi-supine or supine position)~~: taken in triplicate pre-dose on Day 1 and duplicate at all other measurement time points~~.

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 5

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and duplicate at all other measurement time points.

Amended Text:

5. 12-lead ECGs to be measured in triplicate at pre-dose on Day 1, after 5 minutes of rest in the semi-supine or supine position and ~~duplicate~~ **single measurements** at all other ~~measurement~~ time points.

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 7

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

7. Samples for clinical laboratory tests to be collected in the morning prior to receiving study treatment and after an overnight fast of at least 8 hours.

Amended Text:

7. Samples for clinical laboratory tests to be collected **prior to dosing (if applicable)** ~~in the morning prior to receiving study treatment and after an overnight fast of at least 8 hours~~.

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 8

- Rationale: To reduce complexity and visit burden for subjects; to update the subject population in Parts 1 and 2 to include women of child bearing potential.

Original Text:

8. Female subjects at screening and pre-dose Day 1: serum hCG pregnancy test; all other time points: serum hCG or urine pregnancy test.

Amended Text:

8. Female subjects at screening ~~and pre-dose Day 1~~: serum hCG pregnancy test; all other time points: serum hCG or urine pregnancy test. **(Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)**

Section 7.1, Time and Events Tables, Tables 11, 13, and 15, Footnote 11

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

11. On extended PK/dosing days (Days 1, 29, and 57), PK samples will be collected at pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible) and at 1, 2, and 3 hours post-dose. PK samples should

be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded.

Amended Text:

11. On extended PK/dosing days (Days 1, 29, and 57), PK samples will be collected at pre-dose (within 15 to 30 minutes prior to dosing; prefer sample as close to pre-dose time point as possible) and at 1, 2, and 3 hours post-dose. PK samples should be collected as close to the exact nominal time as possible. The exact time of each PK blood collection should be recorded. **PK sampling for the optional Japanese Part 2 sub-study may be detailed in the Japan country-specific protocol amendment/supplement.**

Section 7.1, Time and Events Tables, Tables 10, 11, 13, and 15, Footnote 12

- Rationale: To provide minor edits for clarity

Original Text:

12. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

Amended Text:

12. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb **as well as HBV RNA, HBcrAg, and/or IDO** may be analyzed from the archived ~~plasma~~ sample**s**.

Section 7.1, Time and Events Tables, Tables 12, 14 and 16, Row 12

- Rationale: To update the subject population in Parts 1 and 2 to include women of child bearing potential

Original Text:

Pregnancy test (as appropriate)[6]					X	X

Amended Text:

Pregnancy test (as appropriate)[6]			**X**	**X**	X	X

Section 7.1, Time and Events Tables, Tables 12, 14 and 16, Footnote 1

- Rationale: To provide minor edits for clarity

Original Text:

1. Adverse events will be collected from the time of informed consent and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Amended Text:

1. Adverse events will be collected from the **first dose of study treatment** ~~time of informed consent~~ and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Section 7.1, Time and Events Tables, Tables 12, 14, and 16, Footnote 2

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

2. Temperature and respiration rate (single measurement); blood pressure and heart rate (after 5 minutes of rest in the semi-supine or supine position): taken duplicate at all measurement time points.

Amended Text:

2. Temperature and respiration rate (single measurement); blood pressure and heart rate (**single measurement** after 5 minutes of rest in the semi-supine or supine position)~~: taken duplicate at all measurement time points~~.

Section 7.1, Time and Events Tables, Tables 12, 14, and 16, Footnote 3

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

3. 12 lead ECGs to be measured in duplicate after 5 minutes of rest in the semi-supine or supine position.

Amended Text:

3. **Single** 12 lead ECGs ~~to~~ **will** be measured ~~in duplicate~~ after 5 minutes of rest in the semi-supine or supine position.

Section 7.1, Time and Events Tables, Tables 12, 14 and 16, Footnote 5

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

5. Samples for clinical laboratory tests to be collected in the morning after an overnight fast of at least 8 hours.

Amended Text:

5. Samples for clinical laboratory tests to be collected ~~in the morning~~ after **vital sign and ECG assessments** ~~an overnight fast of at least 8 hours~~.

Section 7.1, Time and Events Tables, Tables 12, 14 and 16, Footnote 9

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

9. On PK days (Day 169 / Early Termination), collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded.

Amended Text:

9. On PK days (Day 169 / Early Termination), collect the PK sample after completion of vital sign assessments. The exact time of each PK blood collection should be recorded. **PK sampling for the optional Japanese Part 2 sub-study may be detailed in the Japan country-specific protocol amendment/supplement.**

Section 7.1, Time and Events Tables, Tables 12, 14 and 16, Footnote 10

- Rationale: To provide minor edits for clarity

Original Text:

10. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb may be analyzed from the archived plasma sample.

Amended Text:

10. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb **as well as HBV RNA, HBcrAg, and/or IDO** may be analyzed from the archived ~~plasma~~ sample**s**.

Section 7.1, Time and Events Tables, Tables 12, 14, and 16 (Footnote 13) and Tables 11, 13, and 15 (Footnote 15)

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

13. or 15. Subjects will be offered a meal (e.g., bagged or canteen) after completion of all study procedures.

Amended Text:

13. or 15. Subjects will be offered a meal (e.g., bagged or canteen **[or reimbursed]**) after completion of all study procedures.

Section 7.2, Screening and Critical Baseline Assessments, New Sentence

Original Text:

Not applicable

Amended Text:

Subjects who screen failed under previous versions of the protocol may be re-screened.

Section 7.3.1, Adverse Events and Serious Adverse Events, new Sentence 2

- Rationale: To provide minor edits for clarity

Original Text:

Not applicable.

Amended Text:

The severity of an AE is graded according to the DAIDS table in Appendix 3 (Section 12.3.5.1).

Section 7.3.1.1, Time Period and Frequency for Collecting AE and SAE Information, Bullet 2

- Rationale: to provide minor edits for clarity

Original Text:

- Adverse events will be collected from the time of informed consent until the final follow-up contact (Section 7.3.1.3) as specified in the Time and Events Table (Section 7.1).

Amended Text:

- Adverse events will be collected from the time of ~~informed consent~~ **first dose of study treatment** until the final follow-up contact (Section 7.3.1.3) as specified in the Time and Events Table (Section 7.1).

Section 7.3.2, Pregnancy, Paragraph 1, Sentence 1

Rationale: To update the subject population in Parts 1 and 2 to include women of child bearing potential

Original Text:

Females of reproductive potential are not permitted in this study.

Amended Text:

Females of reproductive potential are ~~not~~ permitted in this study.

Section 7.3.4, Injection Site Reactions, Paragraph 2

- Rationale: to provide minor edits for clarity

Original Text:

Injection site reactions will be graded according to the criteria provided in the Division of AIDS (DAIDS) grading table (see Appendix 3, Section 12.3.5.1).

Amended Text:

Injection site reactions will be graded according to the criteria provided in the ~~Division of AIDS (~~DAIDS~~)~~ grading table (see Appendix 3, Section 12.3.5.1).

Section 7.3.5, Vital Signs, Bullet 1, Sub-bullets 1-2 2

Original Text:

- Temperature and respiration rate will be collected as single measurements.
- Systolic and diastolic blood pressure and heart rate will be collected in triplicate at the Screening visit and pre-dose on Day 1 and in duplicate at all other time points.

Amended Text:

- **Systolic and diastolic blood pressure**, **heart rate,** ~~T~~**t**emperature**,** and respiration rate will be collected as single measurements.
- ~~Systolic and diastolic blood pressure and heart rate will be collected in triplicate at the Screening visit and pre-dose on Day 1 and in duplicate at all other time points.~~

Section 7.3.6, Electrocardiogram, Bullet 1, Sub-bullet 2

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

- Triplicate 12-lead ECGs will be obtained at the Screening visit and pre-dose on Day 1. Duplicate 12-lead ECGs will be obtained at all other time points.

Amended Text:

- Triplicate 12-lead ECGs will be obtained at ~~the Screening visit and~~ pre-dose on Day 1. ~~Duplicate~~ **Single** 12-lead ECGs will be obtained at all other time points.

Section 7.3.7, Holter, All text

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

7.3.7. Holter

Continuous cardiac telemetry (Holter monitoring) will be performed in Part 1 as specified in the Time and Events Table (Section 7.1, Table 9). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

Start date and time, stop date and time, interpretation, and nature of abnormality, if any, will be captured in the study database. Analysis of the Holter tapes will consider the following:

- Heart rate (bradycardia and tachycardia)
- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, supraventricular tachycardias, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrioventricular conduction defects
- Atrial fibrillation and flutter

Amended Text:

~~7.3.7. Holter~~

~~Continuous cardiac telemetry (Holter monitoring) will be performed in Part 1 as specified in the Time and Events Table (Section 7.1, Table 9). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.~~

~~Start date and time, stop date and time, interpretation, and nature of abnormality, if any, will be captured in the study database. Analysis of the Holter tapes will consider the following:~~

- ~~Heart rate (bradycardia and tachycardia)~~
- ~~Normal and aberrant beats~~
- ~~Number of supraventricular contractions, premature atrial contractions, supraventricular tachycardias, premature ventricular contractions, couplets, triplets, and ventricular tachycardias~~
- ~~Atrioventricular conduction defects~~
- ~~Atrial fibrillation and flutter~~

Section 7.3.8, Clinical Safety Laboratory Assessments (new heading number)

Rationale: To provide minor edits for clarity

Original Text:

7.3.8. Clinical Safety Laboratory Assessments

Amended Text:

7.3.~~8~~**7**. Clinical Safety Laboratory Assessments

Section 7.3.8 Clinical Safety Laboratory Assessments, Paragraph 1, Sentences 2 and 3

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

Fasting is not required for laboratory testing at the Screening visit. For all other laboratory time points, a minimum 8-hour fast is required prior to blood and urine sampling for laboratory tests.

Amended Text:

Fasting is not required for laboratory testing ~~at the Screening visit. For all other laboratory time points, a minimum 8-hour fast is required prior to blood and urine sampling for laboratory tests~~.

Section 7.3.8 Clinical Safety Laboratory Assessments, Table 17, Other Screening and/or Follow-up tests,

- Rationale: To provide minor edits for clarity

Original Text:

- HIV, HCV antibody, HDV antibody

Amended Text:

- HIV, HCV ~~antibody~~, HDV ~~antibody~~

Section 7.3.8 Clinical Safety Laboratory Assessments, Table 17, Other Screening and/or Follow-up tests, New bullet added at end of the list

- Rationale: To provide minor edits for clarity

Original Text:

Not applicable

Amended Text:

- **HBV RNA, HBcrAg, and/or IDO may be analyzed from archived samples**

Section 7.3.8 Clinical Safety Laboratory Assessments, Table 17, New abbreviations added to footnote

- Rationale: To provide minor edits for clarity

Original Text:

Not applicable

Amended Text:

HBcrAg = hepatitis B core-related antigen

IDO = indoleamine 2,3 dioxygenase,

Section 7.3.8 Clinical Safety Laboratory Assessments, Table 17, Footnote 1.

- Rationale: To reduce complexity and visit burden for subjects.

Original Text:

1. Fasting is not required at the Screening visit. A minimum 8-hour overnight fast is required for all other protocols-specified laboratory assessments.

Amended Text:

1. Fasting is not required **for laboratory testing** ~~at the Screening visit. A minimum 8-hour overnight fast is required for all other protocols-specified laboratory assessments~~.

Section 7.6, Biomarker(s)/Pharmacodynamic Markers, Paragraph 2, Sentence 3

- Rationale: To provide minor edits for clarity and addition of HBV RNA

Original Text:

The archive samples may also be used for studying biomarkers that may be affected by treatment, such as hepatitis B core-related antigen (HBcrAg) or indoleamine 2,3 dioxygenase (IDO).

Amended Text:

The archive samples may also be used for studying biomarkers that may be affected by treatment, such as ~~hepatitis B core-related antigen (~~HBcrAg~~)~~, **HBV RNA** or indoleamine 2,3 dioxygenase (IDO).

Section 9. 1 Hypotheses and Section 9.4.1 Primary Analysis

- Rationale: To make edits for typographical error

Original text:

A subject will be considered a responder if there is at least 1.5 times log 10 copies/mL reduction of HBsAg levels from baseline anytime during the study.

Amended text:

A subject will be considered a responder if there is at least 1.5 times log 10 ~~copies~~**IU**/mL reduction of HBsAg levels from baseline anytime during the study.

Section 9.2.1, Sample Size Assumptions, Paragraph 2

- Rationale: To provide correctiosn to the statistical simulations

Original Text:

Assuming 3 dose levels and 2 dosing regimens are selected in Part 2, the probability of declaring success of an inefficacious treatment arm (with RR ≤5%) is less than 4%. On the other hand if an active treatment arm has a 30% RR, the probability of selecting the treatment arm is at least 80% under the model assumption. Appendix 6 (Section 12.6) details the operating characteristics of the design.

Amended text:

Assuming 3 dose levels and 2 dosing regimens are selected in Part 2, the probability of declaring success of an inefficacious treatment arm (with RR ≤5%) is less than 4%. On the other hand if an active treatment arm has a 30% RR, the probability of selecting the treatment arm is at least **95**~~80~~% under the model assumption. Appendix 6 (Section 12.6) details the operating characteristics of the design.

Section 9.2.1, Sample Size Assumptions, Paragraph 1

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.

Original Text:

A sample size of approximately 8 HBV subjects (6 active:2 placebo) in each cohort should be sufficient to provide useful estimates of inter subject variability for GSK3389404 PK parameters and initial safety and PD assessments. Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of observing AEs. With 6 subjects receiving each dose of active study treatment, if the true adverse outcome rate is 5%, the chance of seeing at least 1 adverse outcome at a given dose is 26%. Similarly if the true adverse outcome rate is 20%, the chance of seeing at least 1 adverse outcome at a given dose is 74%. This level of predictivity is deemed adequate within this early phase setting prior to commencing to Part 2 (multiple dose, dose-ranging).

Amended Text:

A sample size of ~~approximately~~ **at least** ~~8~~ **4** HBV subjects **(3 receiving active treatment** (:~~2~~**1** placebo) in each cohort should ~~be sufficient to~~ provide ~~useful~~ **preliminary** estimates of inter subject variability for GSK3389404 PK parameters and initial safety and PD assessments. ~~Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of observing AEs. With 6 subjects receiving each dose of active study treatment, if the true adverse outcome rate is 5%, the chance of seeing at least 1 adverse outcome at a given dose is 26%. Similarly if the true adverse outcome rate is 20%, the chance of seeing at least 1 adverse outcome at a given dose is 74%. This level of predictivity is deemed adequate within this early phase setting prior to commencing to Part 2 (multiple dose, dose-ranging).~~

Section 9.3.2 Definition of Baseline

- Rationale: To reduce complexity and visit burden for subjects

Original Text:

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 (e.g., triplicate blood pressure, heart rate, and 12-lead ECGs), the average of these assessments will be used as the baseline.

Amended Text:

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 ~~(e.g., triplicate blood pressure, heart rate, and 12-lead ECGs)~~, the average of these assessments will be used as the baseline.

Section 9.3.3, Interim Analysis

- Rationale: To provide minor edits for clarity

Original Text:

9.3.3 Interim Analysis

Amended Text:

9.3.3 Interim Analysis **and Final Analysis**

Section 9.3.3, Interim Analysis, Part 1, Paragraph 1, Sentence 2

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.

Original Text:

However, a preliminary PK analysis will be performed after each dose level is completed and the Dose Escalation Committee (Section 10.8.1) will review preliminary safety tolerability, PK and PD data (through Day 3 for at least 4 subjects that received GSK3389404) prior to each dose escalation and prior to initiation of Part 2.

Amended Text:

However, a preliminary PK analysis will be performed after each dose level is completed and the Dose Escalation Committee (Section 10.8.1) will review preliminary safety tolerability, PK and PD data (through Day 3 for at least **43** subjects that received GSK3389404) prior to each dose escalation and prior to initiation of Part 2.

Section 9.3.3, Interim Analysis, Part 1, Paragraph 2, Sentence 1

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.

Original Text:

The relationship between dose levels, plasma GSK3389404 exposure, and associated variability will be characterized by a power model once PK data are available from at least 2 dose levels.

Amended Text:

The relationship between dose levels, plasma GSK3389404 exposure, and associated variability will be characterized by a power model ~~once~~ **if 3 or more subjects'** PK data are available from at least 2 dose levels.

Section 9.3.3, Interim Analysis, Part 2

- Rationale: To provide edits for clarity

Original Text:

Part 2

Amended Text:

Part 2 **Interim Analysis**

New Sections 9.3.3.1, 9.3.3.2, and 9.3.3.3

Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

Not applicable

Amended Text:

9.3.3.1. Part 2: Primary Analysis

In Part 2, the primary analysis will be conducted once the last randomized subject in the sentinel group and remainder of subjects have completed the Day 85 visit. Treatment assignment will be unblinded for subjects included in the analysis. The results of this analysis will be used to characterize safety, tolerability and identify efficacious dose and dosing regimen of GSK3889404.

9.3.3.2. Optional Japanese Part 2 Sub-Study Analysis

Details of the analysis of the optional Japanese Part 2 sub-study may be found in the Japanese country-specific protocol amendment/supplement. If applicable, the analysis of optional Japanese Part 2 sub-study will be conducted once the last randomized Japanese subject has completed the Day 85 and/or Day 169 visit. Treatment assignment for the optional Japanese Part 2 sub-study cohorts will be unblinded. Depending on the timing of the last Japanese subject to finish the Day 85 visit, the analysis may or may not be reported together with the Primary analysis.

9.3.3.3. Part 2: End of Study Analysis

The end of study analysis for Part 2 will be conducted once the last randomized subject (Sentinel, remainder of subjects, and the Japan sub-study subjects if applicable) has completed the Day 169 visit.

Section 9.4.1, Primary Analyses, Efficacy and Section 12.6.2 Statistical Modeling

- Rationale: To provide corrections to the statistical simulations

Original text:

Since it is not expected to have any responder in the placebo arm, posterior distribution of RRs is generated separately from a Beta distribution using uniform prior, i.e., Beta (1,1). Placebo injections will be given in different dosing regimens (according to the corresponding active treatment group) for the purpose of maintaining the blind. However, all placebo subjects across dosing regimens will be combined in 1 group for this analysis, since no difference in RR is expected if placebo is administered in different dosing regimens.

Amended text:

Since it is not expected to have any responder in the placebo arm, posterior distribution of RRs is generated separately from a Beta distribution ~~using uniform prior~~, i.e., Beta (**0.**1,**0.**1). Placebo injections will be given in different dosing regimens (according to the corresponding active treatment group) for the purpose of maintaining the blind. However, all placebo subjects across dosing regimens will be combined in 1 group for this analysis, since no difference in RR is expected if placebo is administered in different dosing regimens.

Section 9.4.1, Primary Analyses, Last Paragraph

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

The primary efficacy analysis of Part 2 will be performed after all ongoing subjects in Part 2 complete the Day 85 visit. At that time the database will be unblinded. Other primary analyses as mentioned above will also be performed. The end of study analysis will be performed after all ongoing subjects in Part 2 complete the Day 169 visit.

Amended Text:

The primary efficacy analysis of Part 2 will be performed after all ongoing subjects in Part 2 complete the Day 85 visit **(may or may not include the Japanese subjects from the optional Japanese Part 2 sub-study)**. At that time the database will be unblinded. Other primary analyses as mentioned above will also be performed. ~~The end of study analysis will be performed after all ongoing subjects in Part 2 complete the Day 169 visit.~~ **Details will be included in the RAP.**

Section 10.8.1, dose Escalation Committee, Paragraph 1, Last Sentence

- Rationale: To provide minor edits for clarity

Original Text:

The GSK study team will remain unblinded throughout Part 1 of the study as detailed in Section 6.5.

Amended Text:

The GSK study team will remain unblinded **at an aggregate level** throughout Part 1 of the study as detailed in Section 6.5.

Section 10.8.1, dose Escalation Committee, Paragraph 2, Sentences 2 and 3

- Rationale: To reduce sample size from 8 subjects (6 active:2 placebo) to 4 subjects (3 active:1 placebo) in Part 1.

Original Text:

Dose escalation decisions will be based on data through Day 3 obtained from at least 4 subjects receiving GSK3389404 at the prior dose level. The review data set will include listings for AEs, flagged vital signs, flagged findings during continuous cardiac monitoring (Holter), ECGs, laboratory findings (including liver function tests), and PK results derived from 24-hour plasma profiles, together with any available PD data (HBsAg levels and HBV DNA).

Amended Text:

Dose escalation decisions will be based on data through Day 3 obtained from at least **43** subjects receiving GSK3389404 at the prior dose level. The review data set will include listings for AEs, flagged vital signs, ~~flagged findings during continuous cardiac monitoring (Holter),~~ ECGs, laboratory findings (including liver function tests), and PK results derived from 24-hour plasma profiles, together with any available PD data ~~(HBsAg levels and HBV DNA).~~

Section 11, References, Delete 2 References

- Rationale: To provide minor edits for clarity

Original Text:

Liaw Y-F, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu DJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61.

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD Guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; 63:261-83.

Amended Text:

~~Liaw Y-F, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu DJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531-61.~~

~~Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD Guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; 63:261-83.~~

Section 12.1, Appendix 1, Abbreviations and Trademarks, DAIDS

- Rationale: To provide minor edits for clarity

Original Text:

DAIDS	Division of Autoimmune Disorders
MCMC	Proc Markov Chain Monte Carlo

Amended Text:

DAIDS	Division of ~~Autoimmune~~ ~~Disorders~~ **Allergy and Infectious Diseases**
MCMC	Markov Chain Monte Carlo

Section 12.1, Appendix 1, Abbreviations and Trademarks, 3 new abbreviations added

- Rationale: To provide minor edits for clarity

Original Text:

Not applicable

Amended Text:

HBcrAg	**hepatitis B core-related antigen**

IDO	**indoleamine 2,3 dioxygenase**

Section 12.4.1 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential, Paragraph 1, Paragraph 2, New Paragraph 3 added, and Item 1.

- Rationale: To update the subject population in Parts 1 and 2 to include women of child bearing potential

Original Text:

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable).

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study treatment until [at least five half-lives of study treatment OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study treatment.

1.Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.

Amended Text:

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable) and for female subjects of reproductive potential (FRP).

Male subjects with female partners of child bearing potential **and female subjects of child bearing potential** must comply with the following contraception requirements **from either** the time of first dose of study treatment **(males) or from at least 28 days prior to the first dose of study treatment (FRP)** until **the final Follow-up visit** ~~[at least five half-lives of study treatment OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study treatment~~.

This list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1.**Male v**asectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's ~~.~~ review of **male** subject's (**or female subject's male partner prior to the female subject's entry into the study)** medical records, medical examination and/or semen analysis, or medical history interview. **This documentation may be provided by male subjects, by female subjects on behalf of their partner, or by her partner.**

Appendix 12.5, Country Specific Requirements

- Rationale: To update the overall design and types/numbers of subjects that will be enrolled given the addition of an optional Japanese Part 2 sub-study.

Original Text:

No country-specific requirements exist.

Amended Text:

If Japan conducts the optional Part 2 sub-study, Japan-specific requirements will be specified in a country-specific amendment/supplement protocol. Otherwise, **n**~~N~~o country-specific requirements exist.

Appendix 12.6, Section 12.6.3, Success Criteria, 1st paragraph

Rationale: To provide corrections to the statistical simulations

Original Text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 80%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥80%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Amended Text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least **95**~~80~~%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥**95**~~80~~%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Appendix 12.6, Section 12.6.4, Scenarios for Testing, Table 18, Row 7

Rationale: To provide minor edits for clarity and typographical errors

Original Text:

Total monthly dose of 240 mg divided bi-weekly (i.e., 120 mg bi-weekly)	240BW	10

Amended Text:

Total monthly dose of ~~2~~**480** mg divided bi-weekly (i.e., ~~1~~**240** mg bi-weekly)	~~2~~**480**BW	10

Appendix 12.6, Section 12.6.5, Simulations

Rationale: To provide corrections to the statistical simulations

Original Text:

Sensitivity of sample size is also provided using different cutoff points for PoS (e.g. 75%, 80%, 85% and 90%)

The above operating characteristics are also calculated for pair-wise comparison (i.e., without any model, based on difference in posterior distributions of individual treatment arm against placebo). In most of the scenarios, the decision of selecting an active treatment group is in agreement by both the methods. However, BLRM provided better operating characteristics (larger power and tighter CI). The probability of selecting an inefficacious treatment group is lower in BLRM compared to pair-wise method. The BLRM was not able to select the efficacious treatment group under Scenario 7, 8 and 9, where there is no monotonic relationship between dose and response. These scenarios are unlikely to happen in real life.

Simulation results for all scenarios are summarized in Table 20 to Table 28.

A cutoff point of 95% for PoS seems to provide reasonable probability for selecting an efficacious dose group given the sample size of this study.

.Amended Text:

Sensitivity of sample size is also provided using different cutoff points for PoS (e.g. **85%, 90%, 95%, and 98%** ~~75%, 80%, 85% and 90%~~).

The above operating characteristics are also calculated for pair-wise comparison (i.e., without any model, based on difference in posterior distributions of individual

treatment arm against placebo, **both with Beta (0.1, 0.1) as prior distribution**). In most of the scenarios, the decision of selecting an active treatment group is in agreement by both the methods. However, BLRM provided better operating characteristics (larger power and tighter CI). The probability of selecting an inefficacious treatment group is lower in BLRM compared to pair-wise method. The BLRM was not able to select the efficacious treatment group under Scenario 7, 8 and 9, where there is no monotonic relationship between dose and response. These scenarios are unlikely to happen in real life.

Simulation results for all scenarios are summarized in Table 20 to Table 28.

A cutoff point of **95**~~80~~% for PoS seems to provide reasonable probability for selecting an efficacious dose group given the sample size of this study.

Appendix 12.6, Section 12.6.5, Simulations, Table 20

Rationale: To provide corrections to the statistical simulations

As all contents of the table were changed, tracked changes are not provided in the below tables

Original:

Table 29 Simulation Results From Scenario 1

	Scenario 1		**No Treatment Effect** (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 5, 5, 5, 5, 5, 5)						
	Treatment	**Posterior RR (%)**	**90% CI**	**PoS[1]**	**Decision[2] (Select dose)**	**Power[3]** **Cutoff Points**			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.69	(2.17,27.33)						
	120W	12.51	(2.08,29.93)	51.75	No	25.3	15.9	4.1	3.1
	120BW	12.56	(2.1,30.01)	51.75	No	25.1	16	5.3	5.1
	240W	12.7	(2.14,30.25)	52.27	No	25.4	15.2	4.4	4.2
	240BW	12.22	(1.97,29.52)	50.76	No	21.4	15.2	5.1	4.6
	480W	12.47	(2.04,29.9)	51.71	No	25.7	17.4	4.2	3.8
	480BW	12.57	(2.1,30.03)	51.86	No	24.5	16	5.3	5
BLRM	PBO	11.69	(2.17,27.34)						
	120W	5.6	(0.76,15.26)	0.4	No	3.3	2.2	0.8	3.3
	120BW	5.57	(0.77,15.16)	0.3	No	4.5	3.5	1.5	4.5
	240W	3.92	(0.72,9.76)	0	No	1.5	0.5	0	1.5
	240BW	3.95	(0.78,9.72)	0.1	No	1.5	0.5	0.2	1.5
	480W	5.7	(0.75,15.65)	0.4	No	3.1	2.1	1	3.1
	480BW	5.73	(0.79,15.57)	0.5	No	4.8	3.6	1.2	4.8

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly
1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 30 Simulation Results From Scenario 2

	Scenario 2		All of the active treatment groups are equally effective (low effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 20, 20, 20, 20, 20, 20)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.53	(2.09,27.11)						
	120W	25.26	(8.91,46.38)	77.13	No	72.6	55.3	47.4	39.4
	120BW	25.27	(8.94,46.36)	77.25	No	73.4	53.9	45.2	37
	240W	25.52	(9.09,46.66)	77.98	No	75.6	54.2	45.2	37.8
	240BW	24.58	(8.54,45.51)	75.98	No	69.7	51.6	42.6	35.6
	480W	24.87	(8.68,45.91)	76.77	No	73.1	54.2	46.5	37.3
	480BW	24.84	(8.59,45.94)	77.26	No	73.9	54.4	45.1	37.5
BLRM	PBO	11.53	(2.09,27.12)						
	120W	20.88	(8.14,37.81)	72.07	No	55.9	48.6	38.8	29.8
	120BW	20.64	(8.03,37.46)	71.62	No	54.4	45.5	36.5	26.7
	240W	19.32	(9.32,31.7)	73.28	No	59.2	47.8	39.6	27.3
	240BW	19.02	(9.12,31.32)	72.73	No	59.1	47	39.5	25.5
	480W	20.56	(7.95,37.39)	71.86	No	55.9	46.7	37.1	27.2
	480BW	20.16	(7.7,36.87)	71.39	No	54.2	46.4	37	24.8

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly
1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 31 Simulation Results From Scenario 3

	Scenario 3		All of the active treatment groups are equally effective (medium effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 30, 30, 30, 30, 30, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pai	PBO	11.63	(2.12,27.28)						

	Scenario 2		All of the active treatment groups are equally effective (low effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 20, 20, 20, 20, 20, 20)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	120W	33.96	(14.91,56.13)	87.1	Yes	89.2	75	70.6	58.1
	120BW	33.05	(14.19,55.21)	86.4	Yes	86.6	73.6	70.4	58.9
	240W	32.82	(14.03,54.96)	86.07	Yes	87.2	72.8	68.7	56.6
	240BW	33.63	(14.61,55.82)	86.79	Yes	88.3	74.1	71.1	59.2
	480W	33.56	(14.61,55.69)	86.51	Yes	87.6	74.1	70	59.2
	480BW	33.07	(14.23,55.19)	86.56	Yes	88.3	76.2	70.7	58.6
BLRM	PBO	11.64	(2.12,27.28)						
BLRM	120W	30.6	(15.05,48.96)	85.75	Yes	80.4	75.6	69.1	57.9
BLRM	120BW	30.3	(14.76,48.72)	86.06	Yes	80.2	75	68.3	56.8
BLRM	240W	29.47	(17.09,43.47)	88.04	Yes	84.7	79.6	71.3	61.4
BLRM	240BW	29.27	(16.92,43.26)	88.19	Yes	85.7	80.1	74.2	62.9
BLRM	480W	30.33	(14.79,48.74)	85.92	Yes	80.9	75.4	68.7	57.8
BLRM	480BW	30.22	(14.77,48.54)	85.83	Yes	81.4	77	68.5	57.2

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 32 Simulation Results From Scenario 4

	Scenario 4		Larger effect in higher dose group (bi-weekly dosing regimen is more efficacious than weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 15, 20, 25, 30, 35)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.6	(2.14,27.2)						
Pairwise Comparison	120W	16.22	(3.79,35.04)	60.91	No	42.2	26.9	13.9	12.4
Pairwise Comparison	120BW	20.68	(6.17,40.8)	69.82	No	61.9	43.3	29.7	25
Pairwise Comparison	240W	25.23	(8.86,46.38)	77.12	No	72.7	55.7	45.7	37.6
Pairwise Comparison	240BW	29.57	(11.72,51.37)	82.7	Yes	82.6	64.8	59.5	49.5
Pairwise Comparison	480W	33.52	(14.49,55.77)	86.83	Yes	89.2	73.4	70.1	59.2
Pairwise Comparison	480BW	37.5	(17.52,59.93)	90.53	Yes	93.4	82.7	80.1	68.3
BLRM	PBO	11.6	(2.14,27.19)						
BLRM	120W	11.82	(3.6,24.34)	51.31	No	24.9	18.6	12.2	6.1
BLRM	120BW	15.15	(5.12,29.57)	60.12	No	35.5	28.5	21.5	12.5
BLRM	240W	18.05	(8.31,30.37)	69.86	No	53.3	44.6	35	24.9

	Scenario 4		Larger effect in higher dose group (bi-weekly dosing regimen is more efficacious than weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 15, 20, 25, 30, 35)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	240BW	22.89	(11.69,36.35)	79.36	No	70.5	61.8	51.2	40.3
	480W	30.47	(14.2,49.86)	85.05	Yes	80.4	74.5	66.3	55.5
	480BW	36.93	(18.95,57.08)	91.12	Yes	90.4	87	82.4	72.5

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 33 Simulation Results From Scenario 5

	Scenario 5		Larger effect in higher dose group (weekly dosing regimen is more efficacious than bi-weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 15, 10, 25, 20, 35, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.44	(2.07,26.95)						
	120W	21.33	(6.5,41.66)	71.63	No	63	45.5	33.9	28.2
	120BW	16.21	(3.78,35.03)	61.39	No	42.9	28.4	15	13.5
	240W	29.28	(11.47,51.09)	83.02	Yes	83.7	66.7	60	49.2
	240BW	24.92	(8.78,45.89)	76.38	No	70.1	53.1	44	37.8
	480W	37.93	(17.84,60.38)	90.49	Yes	92.3	82.6	80.9	70.8
	480BW	32.9	(14.16,54.96)	86.27	Yes	87.6	74.1	70	59.3
BLRM	PBO	11.44	(2.07,26.95)						
	120W	15.55	(5.28,30.22)	61.72	No	38.1	30.4	21.8	13
	120BW	11.76	(3.55,24.27)	51.74	No	22.6	17.6	11	5.7
	240W	23.26	(11.96,36.77)	80.14	No	72.8	65.9	56	43.2
	240BW	17.83	(8.2,30.03)	69.93	No	53.1	43.6	35.7	23.7
	480W	36.98	(19.03,57.09)	90.85	Yes	89.9	85.7	81.4	73.1
	480BW	29.8	(13.86,48.9)	84.19	Yes	77.8	72.3	65.1	54.7

BLRM = Bayesian logistic regression model; BW = bi-weekly' CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 34 Simulation Results From Scenario 6

	Scenario 6		Only 480 mg (highest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 10, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.53	(2.11,27.1)						
	120W	16.73	(4.09,35.67)	61.94	No	44.7	29.2	16.9	14.4
	120BW	16.63	(4,35.58)	62.02	No	44.1	29.2	16.6	15.1
	240W	17.01	(4.19,36.07)	63.07	No	47.4	30.4	17.2	14.9
	240BW	16.83	(4.14,35.79)	62.19	No	43.9	30.7	18.1	15.1
	480W	16.59	(4,35.51)	61.82	No	42.9	26.7	16.9	14.9
	480BW	33.63	(14.64,55.8)	87.03	No	88.8	75	69.9	59.7
BLRM	PBO	11.54	(2.11,27.1)						
	120W	7.37	(1.61,17.36)	35.03	No	8.3	5.4	2.7	1.4
	120BW	11.41	(2.94,24.88)	48.98	No	21.9	15.6	9.4	4.5
	240W	9.01	(2.94,17.97)	43.42	No	15.8	8.6	5.1	1.6
	240BW	14.59	(6,25.96)	61.61	No	39.6	30.4	19.2	12.2
	480W	14.85	(4.38,30.45)	58.11	No	31.9	25.6	18.3	9.9
	480BW	23.81	(9.3,42.65)	75.05	No	62.9	57.2	47.8	36.2

BLRM = Bayesian logistic regression model; CI = credible interval; M = monthly; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 35 Simulation Results From Scenario 7

	Scenario 7		Only 480 mg (highest dose) is efficacious (bi-weekly having medium effect and weekly having small effect) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 20, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.48	(2.08,27.02)						
	120W	16.4	(3.89,35.27)	61.56	No	43.9	27.9	16	14.5
	120BW	16.83	(4.06,35.9)	62.82	No	46	30.3	17	15.5
	240W	16.93	(4.16,35.97)	62.77	No	46.4	32.1	18.1	15.2
	240BW	16.73	(4.01,35.76)	62.67	No	46.4	30.1	17.1	14.8
	480W	25.17	(8.81,46.31)	77.7	No	73.9	52.9	44.2	36.9
	480BW	33.46	(14.51,55.62)	87.03	Yes	88.8	75.2	71	60.4

	Scenario 7		Only 480 mg (highest dose) is efficacious (bi-weekly having medium effect and weekly having small effect) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 20, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
BLRM	PBO	11.48	(2.08,27.02)						
	120W	7.92	(1.85,18.23)	37.57	No	11.4	7.3	4.3	2
	120BW	9.62	(2.37,21.53)	43.8	No	15.1	11.3	7	2.9
	240W	11.45	(4.22,21.6)	52.29	No	25.7	18.7	13.1	5.7
	240BW	14.29	(5.79,25.63)	60.98	No	38.3	29.3	20	11.2
	480W	21.2	(7.71,39.33)	72.07	No	56	47.3	35.9	26.1
	480BW	26.26	(10.88,45.63)	79.38	No	69	62.7	53.7	43.6

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 36 Simulation Results From Scenario 8

	Scenario 8		Only 240 mg (middle dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 30, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.45	(2.07, 26.97)						
	120W	16.08	(3.7,34.87)	61.07	No	42.4	28.6	15.8	14.2
	120BW	16.27	(3.82,35.1)	61.41	No	44.4	29.2	15.2	13.6
	240W	16.72	(4.05,35.7)	62.25	No	45.6	30.6	18.6	17.3
	240BW	34	(14.96,56.15)	86.81	Yes	87.1	75.3	71.5	61.3
	480W	16.49	(3.92,35.4)	61.94	No	44.7	30.4	14.9	13.5
	480BW	16.48	(3.95,35.35)	61.44	No	43.4	30.2	17.9	16.4
BLRM	PBO	11.45	(2.07, 26.97)						
	120W	10.18	(2.48,22.78)	45.95	No	16.1	11.2	7.1	3.4
	120BW	16.85	(5.36,33.34)	63.63	No	40.6	34.5	24.7	15.9
	240W	9.13	(2.93,18.26)	45.03	No	16.9	9.5	5.4	2.3
	240BW	15.35	(6.57,26.77)	64.13	No	44.4	35.3	24.9	15.1
	480W	10.68	(2.68,23.6)	47.18	No	18	13.9	8.8	4.8
	480BW	17.26	(5.55,33.98)	64.46	No	42.6	36.6	26.1	17

	Scenario 8		**Only 240 mg (middle dose) bi-weekly dosing is efficacious** (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 30, 10, 10)				
	Treatment	**Posterior RR (%)**	**90% CI**	**PoS[1]**	**Decision[2] (Select dose)**	**Power[3] Cutoff Points**	

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Table 37 Simulation Results From Scenario 9

	Scenario 9		**Only 120 mg (lowest dose) bi-weekly dosing is efficacious** (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 30, 10, 10, 10, 10)						
	Treatment	**Posterior RR (%)**	**90% CI**	**PoS[1]**	**Decision[2] (Select dose)**	**Power[3] Cutoff Points**			
						75%	80%	85%	90%
Pairwise Comparison	PBO	11.05	(1.88,26.43)						
	120W	16.59	(3.97,35.54)	63.25	No	45.8	31.1	17.1	15
	120BW	33.39	(14.37,55.64)	87.79	Yes	88.9	77.5	74	63.6
	240W	16.91	(4.19,35.89)	63.52	No	47.7	31.3	19	16.6
	240BW	16.56	(3.99,35.45)	62.81	No	45.2	29.8	17.5	16
	480W	16.67	(4,35.67)	63.39	No	45.8	30.9	16.6	15.1
	480BW	16.83	(4.12,35.83)	63.56	No	45.4	29.8	18	15.8
BLRM	PBO	11.05	(1.88,26.43)						
	120W	14.53	(4.19,30.08)	59.18	No	32.7	26.6	16.5	10
	120BW	23.51	(9.04,42.35)	75.75	No	64.4	58.6	49.3	37.1
	240W	9	(2.91,17.98)	44.99	No	16.4	8.7	6	2.7
	240BW	14.54	(6,25.87)	62.7	No	40.8	32.7	22.3	13.2
	480W	7.49	(1.65,17.58)	36.46	No	8.8	6.6	3.9	1.2
	480BW	11.54	(3.06,24.93)	50.19	No	23	17.2	10.7	5.8

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 80%
3. Power is defined as percentage of time PoS >80% over the sample space (i.e., 1000 simulations)

Amended:

Table 38 Simulation Results From Scenario 1

	Scenario 1		No Treatment Effect (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 5, 5, 5, 5, 5, 5)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.86	(0.79,15.93)						
	120W	5.77	(0.68,16.43)	48.13	No	22.3	22.3	17.9	3.5
	120BW	5.71	(0.73,16.13)	47.32	No	20.7	20.7	17.3	4.3
	240W	6.26	(0.76,17.48)	49.78	No	22.6	22.6	18.8	4.9
	240BW	5.88	(0.69,16.67)	48.44	No	21.6	21.6	17.8	3.6
	480W	6.19	(0.8,17.18)	48.94	No	23.3	23.3	18.4	6.1
	480BW	5.69	(0.65,16.26)	47.79	No	21.7	21.7	18.2	4.5
BLRM	PBO	5.91	(0.79,16.21)						
	120W	5.51	(0.74,15.07)	56.39	No	32.7	22.6	9.9	2.0
	120BW	5.53	(0.78,15.01)	56.12	No	29.9	22.0	9.9	2.4
	240W	3.98	(0.76,9.84)	54.55	No	32.9	20.5	7.9	0.6
	240BW	3.86	(0.73,9.58)	53.92	No	31.1	19.0	7.6	0.9
	480W	6.07	(0.89,16.19)	57.82	No	32.4	25.8	13.1	4.2
	480BW	5.69	(0.77,15.52)	57.19	No	30.9	24.8	12.5	2.5

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 39 Simulation Results From Scenario 2

	Scenario 2		All of the active treatment groups are equally effective (low effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 20, 20, 20, 20, 20, 20)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.66	(0.77,15.46)						
	120W	20.54	(6,41.01)	80.5	No	60.6	60.0	50.8	35.1
	120BW	20.82	(6.2,41.3)	80.81	No	61.5	61.1	51.6	34.8
	240W	21.09	(6.35,41.57)	80.5	No	62.8	61.9	50.7	36.7
	240BW	20.57	(6.14,40.83)	80.05	No	59.8	59.0	49.5	33.3

	Scenario 2		All of the active treatment groups are equally effective (low effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 20, 20, 20, 20, 20, 20)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	480W	19.91	(5.73,39.95)	79.03	No	60.2	59.9	49.4	35.3
	480BW	20.86	(6.22,41.3)	80.1	No	61.7	61.1	51.4	35.7
BLRM	PBO	5.71	(0.77,15.73)						
BLRM	120W	20.53	(7.97,37.3)	86.37	No	71.3	65.2	55.2	41.2
BLRM	120BW	20.8	(8.09,37.69)	86.78	No	71.2	64.6	55.3	40.9
BLRM	240W	18.97	(9.07,31.27)	86.79	No	70.7	64.3	56.3	44.4
BLRM	240BW	19.24	(9.28,31.59)	87.13	No	72.8	64.6	55.9	45.8
BLRM	480W	20.3	(7.83,36.97)	85.5	No	70.2	64.5	55.0	40.6
BLRM	480BW	20.58	(8.03,37.33)	85.78	No	69.9	64.1	56.5	41.6

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 40 Simulation Results From Scenario 3

	Scenario 3		All of the active treatment groups are equally effective (medium effect size) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 30, 30, 30, 30, 30, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.27	(0.63,14.82)						
Pairwise Comparison	120W	30.22	(11.56,53.18)	90.59	No	80.4	78.9	65.7	52.5
Pairwise Comparison	120BW	30.47	(11.77,53.41)	91.07	No	81.0	79.6	66.9	53.3
Pairwise Comparison	240W	30.27	(11.62,53.2)	90.09	No	78.1	77.0	65.3	53.7
Pairwise Comparison	240BW	30.85	(12.03,53.79)	90.43	No	79.8	78.1	66.9	53.7
Pairwise Comparison	480W	31.04	(12.04,54.17)	90.8	No	80.8	79.8	68.3	56.0
Pairwise Comparison	480BW	29.97	(11.54,52.67)	89.68	No	78.4	77.1	65.9	52.8
BLRM	PBO	5.32	(0.63,15.09)						
BLRM	120W	30.39	(14.88,48.75)	94.32	No	88.0	82.9	72.4	60.8
BLRM	120BW	30.25	(14.75,48.63)	94.34	No	88.7	81.8	72.2	60.8
BLRM	240W	29.45	(17.05,43.47)	95.32	Yes	90.9	85.1	75.2	64.1
BLRM	240BW	29.41	(17.04,43.4)	95.29	Yes	89.9	85.1	76.0	63.9
BLRM	480W	30.52	(14.92,48.96)	94.1	No	86.9	81.4	73.1	60.5
BLRM	480BW	30.57	(15.05,48.91)	94.02	No	86.5	82.0	72.9	60.7

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 41 Simulation Results From Scenario 4

	Scenario 4		Larger effect in higher dose group (bi-weekly dosing regimen is more efficacious than weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 15, 20, 25, 30, 35)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.42	(0.73,14.94)						
	120W	10.49	(1.91,25.29)	62.61	No	38.1	38.1	31.7	15.7
	120BW	16.37	(4.15,34.77)	74.76	No	53.9	53.6	45.0	26.8
	240W	20.75	(6.16,41.14)	81.02	No	61.4	60.5	51.5	36.6
	240BW	25.88	(9.04,47.74)	86.46	No	72.3	71.5	59.9	45.0
	480W	31.43	(12.49,54.39)	90.2	No	79.3	78.0	68.4	54.1
	480BW	34.46	(14.41,57.92)	92.55	No	84.0	82.6	72.3	60.2
BLRM	PBO	5.47	(0.73,15.21)						
	120W	12.24	(3.78,25.02)	77.56	No	57.9	53.5	40.5	20.1
	120BW	15.55	(5.36,30.08)	81.92	No	64.3	58.2	48.7	30.1
	240W	18.39	(8.52,30.8)	86.96	No	70.9	63.7	55.9	45.4
	240BW	22.96	(11.79,36.35)	90.91	No	79.9	74.1	63.9	54.3
	480W	30.64	(14.45,49.87)	93.16	No	84.9	78.5	70.5	58.6
	480BW	36.44	(18.66,56.44)	95.71	Yes	90.1	86.7	80.1	69.2

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 42 Simulation Results From Scenario 5

	Scenario 5		Larger effect in higher dose group (weekly dosing regimen is more efficacious than bi-weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 15, 10, 25, 20, 35, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%

	Scenario 5		Larger effect in higher dose group (weekly dosing regimen is more efficacious than bi-weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 15, 10, 25, 20, 35, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
Pairwise Comparison	PBO	5.89	(0.79,16.01)						
	120W	15.35	(3.59,33.51)	71.91	No	47.6	47.5	39.4	24.8
	120BW	11.1	(2.15,26.26)	62.23	No	37.0	37.0	30.4	14.5
	240W	25.26	(8.64,47)	85.09	No	69.8	68.6	56.4	40.6
	240BW	20.61	(6.01,41.08)	80.06	No	60.1	59.6	48.8	33.6
	480W	34.72	(14.63,58.19)	92.29	No	82.2	81.0	71.5	58.2
	480BW	29.63	(11.11,52.59)	89.04	No	74.8	73.5	62.9	50.5
BLRM	PBO	5.94	(0.78,16.27)						
	120W	15.25	(5.19,29.7)	80.12	No	59.9	54.1	43.2	26.1
	120BW	12.13	(3.73,24.83)	75.49	No	54.4	48.7	36.6	17.9
	240W	22.52	(11.48,35.84)	90.03	No	77.1	69.2	59.2	47.2
	240BW	18.06	(8.32,30.36)	85.58	No	66.8	60.3	52.1	41.1
	480W	35.7	(18.03,55.74)	95.35	Yes	90.0	85.7	77.4	66.1
	480BW	29.84	(13.75,49.13)	92.59	No	83.6	76.5	66.9	57.2

BLRM = Bayesian logistic regression model; BW = bi-weekly' CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 43 Simulation Results From Scenario 6

	Scenario 6		Only 480 mg (highest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 10, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.87	(0.79,15.98)						
	120W	10.69	(1.94,25.78)	62.31	No	37.2	37.0	30.4	12.7
	120BW	11.31	(2.13,26.85)	63.39	No	38.8	38.7	31.9	16.3
	240W	10.53	(1.97,25.28)	60.78	No	35.5	35.5	29.5	14.6
	240BW	10.35	(1.88,25.04)	60.98	No	35.3	35.3	29.3	13.3
	480W	10.53	(1.94,25.35)	61.14	No	36.8	36.8	31.0	14.1
	480BW	30.59	(11.86,53.5)	89.42	No	77.5	75.8	64.7	50.6
BLRM	PBO	5.92	(0.79,16.22)						
	120W	7.32	(1.61,17.24)	63.74	No	42.8	34.4	19.3	5.6
	120BW	11.45	(2.99,24.92)	72.63	No	51.6	45.2	32.2	15.2

	Scenario 6		Only 480 mg (highest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 10, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	240W	8.71	(2.78,17.53)	69.47	No	48.7	42.0	29.4	11.5
	240BW	14.46	(5.92,25.8)	80.12	No	57.4	53.1	46.3	29.5
	480W	14.24	(4.08,29.58)	77.18	No	55.6	50.3	40.5	21.9
	480BW	23.65	(9.2,42.41)	86.9	No	73.6	66.4	56.9	43.1

BLRM = Bayesian logistic regression model; CI = credible interval; M = monthly; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 44 Simulation Results From Scenario 7

	Scenario 7		Only 480 mg (highest dose) is efficacious (bi-weekly having medium effect and weekly having small effect) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 20, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.87	(0.75,16.07)						
	120W	10.72	(1.97,25.75)	61.57	No	36.0	35.9	29.3	14.5
	120BW	11.17	(2.09,26.61)	62.83	No	37.6	37.5	31.2	16.0
	240W	11.63	(2.31,27.22)	63.58	No	39.7	39.7	31.9	15.6
	240BW	10.33	(1.75,25.33)	61.66	No	35.4	35.3	29.2	12.0
	480W	20.8	(6.04,41.54)	80.43	No	59.3	58.8	49.4	35.5
	480BW	30.47	(11.72,53.52)	89.53	No	77.1	76.1	63.1	50.7
BLRM	PBO	5.92	(0.75,16.3)						
	120W	8.21	(1.95,18.74)	65.9	No	45.8	36.6	21.4	7.1
	120BW	9.72	(2.41,21.68)	69.54	No	48.2	41.4	26.6	11.7
	240W	11.71	(4.35,21.99)	75.37	No	55.6	50.8	39.0	20.5
	240BW	14.19	(5.68,25.54)	80	No	57.1	52.0	45.8	29.5
	480W	21.44	(7.88,39.61)	85.58	No	67.5	62.4	54.7	40.1
	480BW	25.9	(10.63,45.2)	89.37	No	76.2	70.4	59.8	46.9

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 45 Simulation Results From Scenario 8

	Scenario 8		Only 240 mg (middle dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 30, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.4	(0.68,15.04)						
	120W	11.04	(2.04,26.4)	64.38	No	41.0	40.9	33.3	15.2
	120BW	9.94	(1.76,24.3)	61.6	No	37.8	37.7	29.2	12.0
	240W	11.05	(2.07,26.33)	64.22	No	41.1	41.1	34.2	16.0
	240BW	31.46	(12.39,54.59)	90.34	No	78.3	77.6	67.1	56.3
	480W	10.44	(1.94,25.16)	62.3	No	38.3	38.3	32.1	14.4
	480BW	10.67	(1.88,25.83)	63.48	No	39.1	39.0	33.4	15.7
BLRM	PBO	5.46	(0.68,15.33)						
	120W	10.68	(2.74,23.46)	73.45	No	54.8	47.5	31.9	14.2
	120BW	16.98	(5.46,33.5)	82.05	No	65.7	60.4	49.8	32.8
	240W	9.5	(3.19,18.68)	73.12	No	55.6	46.6	34.0	15.6
	240BW	15.38	(6.6,26.82)	82.64	No	64.3	58.6	51.9	36.4
	480W	10.85	(2.82,23.76)	73.32	No	55.2	48.9	32.9	14.7
	480BW	17.12	(5.49,33.79)	82.42	No	65.1	59.7	49.2	33.3

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 46 Simulation Results From Scenario 9

	Scenario 9		Only 120 mg (lowest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 30, 10, 10, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.84	(0.79,15.87)						
	120W	10.47	(1.86,25.38)	61.37	No	35.4	35.4	28.2	14.3
	120BW	31.02	(11.9,54.34)	90.87	No	79.1	77.5	66.3	52.1
	240W	10.6	(1.86,25.73)	62.39	No	36.5	36.5	30.5	13.4
	240BW	10.27	(1.82,24.96)	61.21	No	36.5	36.5	30.6	12.8
	480W	11.23	(2.12,26.65)	63.35	No	38.0	38.0	30.6	15.1
	480BW	10.74	(1.97,25.76)	61.98	No	37.5	37.3	30.4	15.1
B -	PBO	5.89	(0.79,16.13)						

	Scenario 9		Only 120 mg (lowest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 30, 10, 10, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	120W	14.42	(4.15,29.85)	78.21	No	56.9	51.9	38.4	23.4
	120BW	23.62	(9.06,42.55)	87.68	No	74.0	67.7	57.3	44.0
	240W	8.89	(2.88,17.79)	70.22	No	50.0	41.3	29.1	13.1
	240BW	14.44	(5.85,25.85)	80.92	No	61.0	55.3	45.8	31.4
	480W	7.49	(1.68,17.48)	64.06	No	42.2	33.1	20.1	7.6
	480BW	11.39	(2.93,24.87)	73.07	No	51.7	46.0	33.1	14.8

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Section 12.1, Appendix 1 Abbreviations

Rationale: To make edits for clarity

Original Text:

DAIDS	Division of Allergy and Infectious Diseases

Amdended Text

DAIDS	Division of ~~Allergy and Infectious Diseases~~ **Acquired Immune Deficiency Syndrome**

12.7.4. Protocol changes for Amendment 04 (21-OCT-2017) from Protocol Amendment 03 (28-JUN-2017)

Protocol Amendment 4 replaces the protocol amendment 3 dated 28 JUN 2017 and applies to South Korea only.

Protocol Amendment 4 is being implemented for the following reasons:

- To remove females of reproductive potential for Part 1 of study 205670 based on feedback from South Korea MFDS.
    - South Korea MFDS requires 3 months of contraceptive use for women of child-bearing potential after the last dose of investigational product. As Part 1 requires contraceptive use only until Day 60, women of child-

bearing potential for Part 1 has been removed to comply with MFDS requirements.

- To provide edits for clarity.

LIST OF CHANGES

Section 5.1, Inclusion Criteria 4b.

Rationale: To remove females of reproductive potential for Part 1 of study 205670 based on feedback from South Korea MFDS

Original text:

> Females of reproductive potential (FRP), must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until the final Follow-up visit in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Amended text:

> **For Part 2,** Females of reproductive potential (FRP), must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until the final Follow-up visit in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Section 5.1, Exclusion Criteria 18.

Rationale: To remove females of reproductive potential for Part 1 of study 205670 based on feedback from South Korea MFDS

Original text: (not applicable)

Amended text:

18. For Part 1, females of reproductive potential

Section 7.1 Time and Events Table 8. Time and Events Table: Screening: Single Ascending Dose (Part 1) and Multiple Dose (Part 2)

Rationale: To provide edits for clarity. The informed consent is not restricted to the 30 day screening window. The informed consent may be obtained at any time prior to screening of the subject.

Original text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**
Informed Consent	X

Amended text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**
Informed Consent **(obtained any time prior to screening)**	X

Section 7.3.2 Pregnancy

Rationale: To remove females of reproductive potential for Part 1 of study 205670 based on feedback from South Korea MFDS. This statement does not apply for both Parts 1 and 2 of the study.

Original text:

Females of reproductive potential are permitted in this study.

Amended text:

~~Females of reproductive potential are permitted in this study.~~

Appendix 5: Country Specific Requirements

Rationale: To provide edits for clarity. To include South Korea specific requirement

Original text:

If Japan conducts the optional Japanese Part 2 sub-study, Japan-specific requirements will be specified in a country-specific amendment or supplement protocol.

Otherwise, no country-specific requirements exist.

Amended text:

If Japan conducts the optional Japanese Part 2 sub-study, Japan-specific requirements will be specified in a country-specific amendment or supplement protocol.

South Korea will exclude females of reproductive potential in Part 1 only as shown in the country-specific protocol amendment.

Otherwise, no country-specific requirements exist.

12.7.5. Protocol changes for Amendment 05 (06-MAR-2018) from Protocol Amendment 03 (28-JUN-2017)

Protocol Amendment 5 replaces Protocol Amendment 03 (28 JUN 2017) and applies to all study sites.

Protocol Amendment 05 Summary:

Protocol Amendment 5 is being implemented for the following reasons:

- To update the protocol with the treatments to be studied in Part 2

  Rationale: The previous versions of the protocol included flexible language such that the treatments (doses and regimens) and population (HBeAg status) to be studied in Part 2 would be determined after the safety review of Part 1. A request was made that those treatments be explicitly written in a protocol amendment for Part 2. These changes (e.g., treatment details, subject numbers, and statistical sections) were made to satisfy the request from some health authorities/ethics committees.

- To include an optional additional 9-month off-treatment follow up period

  Rationale: An additional 9-month off-treatment follow up period (total 12 months off-treatment period) was added to evaluate a longer period of safety review and efficacy of GSK3389404 in chronic hepatitis B patients

- To provide updates to the pre-clinical and clinical data

  Rationale: Align with pre-clinical data updates (such as the 39-week monkey study, 26-week mouse study) made in the Investigator's Brochure (published January 2018) and to update the dose rationale with preliminary data from Part 1 to select the treatments to be studied in Part 2

- To include management review of unblinded data

  Rationale: Management review of unblinded efficacy data is planned for both Part 1 and Part 2 of the study. For part 1, the review provides early information on potential efficacious dose and dose frequency including the need for dose

escalation. For part 2, the review will facilitate internal governance decision making on project progress and trigger further studies.

- To provide updates in the statistical sections

  Rationale: After selecting the treatments (dose/regimen) for Part 2, the statistical simulations were updated and the statistical assumptions were revised based on the change in total subject number. The statistical sections were also changed to include the addition of the optional additional follow up in Part 2 and the analyses/study definitions as appropriate.

- To provide clarity

  Rationale: Additional text has been added to provide clarity after queries were received by investigators and/or ethics committees. These include- clarification that informed consent is not restricted to the 30 day screening window; clarification on contraceptive use for males with female partners who are currently pregnant; clarification on the use of interferon before and during the study; clarification on PK collection windows based on different site practices

- To make minor edits on typographical errors, formatting changes, and updates to references.

  Note: these changes will not be included in the list of changes below unless a update text change would impact the overall content

LIST OF SPECIFIC CHANGES

Section 1. Protocol Synopsis for study 205670, Overall design, fourth paragraph, first sentence

Rationale: To make edits for clarity, to be consistent throughout protocol

Original text:

Part 2 will be conducted as a multiple-dose, dose-ranging study. Part 2 plans to enroll subjects primarily from the Asia-Pacific region

Amended text:

Part 2 will be conducted as a multiple-dose, dose-ranging study. Part 2 plans to enroll subjects primarily from the Asia-Pacific region, **including Japan.**

Section 1. Protocol Synopsis for study 205670, Overall design, fourth paragraph

Rationale: To update the treatments to be studied in Part 2

Original text:

The dose levels and regimens for Part 2 will be selected after review of safety (at a minimum of adverse events [AEs], laboratory chemistry, hematology, and electrocardiogram [ECG]), PK, and PD data from Part 1 (through Day 3) but will not exceed a total monthly SC dose of 480 mg. For each dose level, the total monthly dose will be the same but divided into once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens for a planned treatment duration of 3 months. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens.

Amended text:

The dose levels and regimens for Part 2 will be selected after review of safety (at a minimum of adverse events [AEs], laboratory chemistry, hematology, and electrocardiogram [ECG]), PK, and PD data from Part 1 (through Day 3) ~~but will not exceed a total monthly SC dose of 480 mg. For each dose level, the total monthly dose will be the same but divided into once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens for a planned treatment duration of 3 months. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens~~. **The treatments selected are 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo.**

Section 1. Protocol Synopsis for study 205670, Treatment arms and duration, 2nd paragraph.

Rationale: To update the treatment and populations to be studied in Part 2and to update text to include an optional additional 9 month off-treatment follow up period

Original text:

In Part 2, two or 3 dose levels each at 2 different dosing regimens are planned and the total study duration, including screening, dosing, and post-treatment follow-up, is not expected to exceed 29 weeks for each subject.

Amended text:

In Part 2, **60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo** ~~two or 3 dose levels each at 2 different dosing regimens~~ are planned and the total study duration, including screening, dosing, and post-treatment follow-up, is not expected to exceed ~~29~~ **65** weeks for each subject.

Section 1. Protocol Synopsis for study 205670, Treatment arms and duration, 2nd paragraph, bullet 2 and 3

Rationale: To update the treatments to be studied in Part 2

Original text:

- An expected study treatment exposure of up to 85 days is planned where subjects will receive multiple SC doses of GSK3389404 (≤480 mg total monthly dose) or placebo at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens.
    - The total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen.

Amended text:

- An expected study treatment exposure of up to 85 days is planned where subjects will receive ~~multiple SC doses of GSK3389404 (≤480 mg total monthly dose) or placebo at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens.~~ **60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly.**
    - ~~The total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks) dosing regimen.~~

Section 1. Protocol Synopsis for study 205670, Treatment arms and duration, 2nd paragraph, sub-bullet of bullet 3, and bullet 5

Rationale: To update the treatments to be studied in Part 2 and to update text to include an optional additional 9 month off-treatment follow up period

Original text:

    - For monthly dosing, subjects will be administered GSK3389404 or placebo as a SC dose on Days 1, 29, and 57.
- A post-treatment follow-up period is planned where subjects will present for study visits on Days 85, 92, 99, 113, 141, and 169.

Amended text:

    - ~~For monthly dosing, subjects will be administered GSK3389404 or placebo as a SC dose on Days 1, 29, and 57.~~
- A post-treatment follow-up period is planned where subjects will present for study visits on Days 85, 92, 99, 113, 141, and 169.

- **An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.**

Section 1. Protocol Synopsis for study 205670, Type and Number of subjects

Rationale: To update the treatments to be studied in Part 2 and to provide updates to the clinical data from Part 1 of the study

Original text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects, and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAgnegative- subjects (or none at all). A decision will be made about the specific CHB population for enrollment in Part 2 after completion of dosing in Part 1 (after review of safety, tolerability, PK, and PD differences between HBeAg status).

Approximately 150 subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, approximately 20 to 40 subjects with CHB are planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range is provided because different countries and sites may be enrolling under the older versions of the protocol.
- In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. The exact number of subjects to be enrolled will be data driven from Part 1 (e.g., safety, tolerability, and PD effects) and will depend on the number of dose levels/regimens selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate14% overall drop-out rate, so that there are approximately 10 evaluable subjects in each of the active treatment group and approximately 12 subjects in placebo.

Amended text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects, and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAg- negative- subjects (or none at all). ~~A decision will be made about the specific CHB population for enrollment in Part 2 after completion of dosing in Part 1 (after review of safety, tolerability, PK, and PD differences between HBeAg status).~~

Approximately ~~150~~ **73** subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, approximately 20 to 40 subjects with CHB ~~are~~ **were** planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range ~~is~~ **was** provided because different countries and sites may **have enrolled** ~~be enrolling~~ under the older versions of the protocol. **Twelve subjects were enrolled for Part 1 and Part 1 has completed enrollment.**
- In Part 2, approximately ~~80~~ **39** subjects with CHB are planned for randomization to study treatment. ~~The exact number of subjects to be enrolled will be data-driven from Part 1 (e.g., safety, tolerability, and PD effects) and will depend on the number of dose levels/regimens selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate14% overall drop-out rate, so that~~ **T**here are approximately 1**1**~~0~~ evaluable subjects in each of the active treatment group**s** and approximately **6**~~12~~ subjects in **the** placebo **group**.

Section 1. Protocol Synopsis for study 205670, Analysis, Part 2, paragraph 1, sentence 4

Rationale: To provide updates in the statistical section due to change in total subject number

Original text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 95%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥95%, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

Amended text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least **90**~~5~~%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥**90**~~5~~%, where RR_{ACT} is the RR in active group, RR_{PBO} is the RR in placebo, and P is the posterior probability.

Section 4.1 Overall Design, Paragraph 4

Rationale: To update the treatments to be studied in Part 2

Original text:

The dose levels and regimens for Part 2 will be selected after a review of Part 1 safety, (at a minimum of adverse events [AEs], laboratory chemistry and hematology and electrocardiogram [ECG]), PK, and PD data (through Day 3) but will not exceed a total monthly dose of 480 mg. For each dose level, the total monthly SC dose will be the same but divided into weekly, bi-weekly (every 2 weeks), or monthly dosing regimens for a planned treatment duration of 3 months. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks**)** dosing regimen. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens.

Amended text:

The dose levels and regimens for Part 2 ~~will be~~ **have been** selected after ~~a review of~~ Part 1 safety, (at a minimum of adverse events [AEs], laboratory chemistry and hematology and electrocardiogram [ECG]), PK, and PD data (through Day 3) **were reviewed** ~~but will not exceed a total monthly dose of 480 mg. For each dose level, the total monthly SC dose will be the same but divided into weekly, bi-weekly (every 2 weeks), or monthly dosing regimens for a planned treatment duration of 3 months. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly (every 2 weeks**)** dosing regimen. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens~~. **The treatments for Part 2 are 60 mg GSK3389404 weekly, 120 mg bi-weekly GSK3389404, 120 mg GSK3389404 weekly or placebo.**

Section 4.1 Overall Design, Paragraph 6

Rationale: To update the treatment and populations to be studied in Part 2

Original text:

Study treatment and post-treatment follow-up Time and Events Tables for weekly, bi-weekly (every 2 weeks), or monthly dosing regimens are provided in Section 7.1.

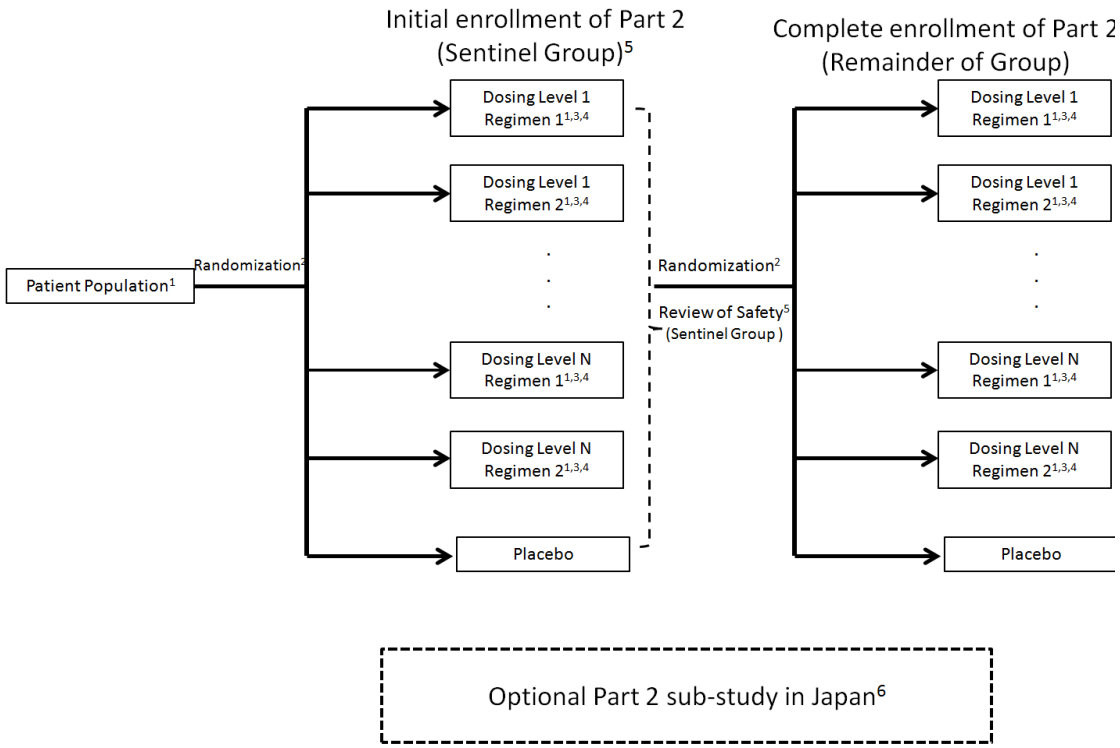
Amended text:

Study treatment and post-treatment follow-up Time and Events Tables for weekly~~,~~ **and** bi-weekly (every 2 weeks)~~, or monthly~~ dosing regimens are provided in Section 7.1.

Section 4.1 Overall Design, Figure 2 and footnotes

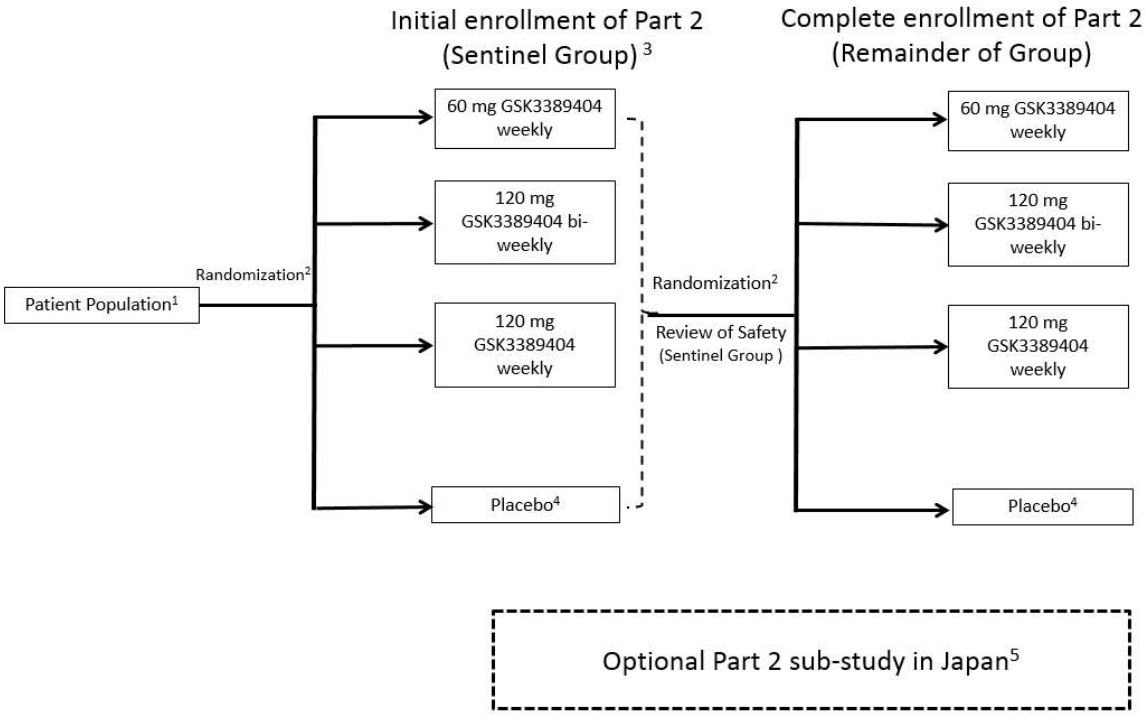
Rationale: To update the treatment and populations to be studied in Part 2 (please note that the figure was amended to include the treatments, a ‘strike-through’ figure was not included in the amended text)

Original text:



6. Hepatitis B virus e-antigen status of the subject population in Part 2 will depend on safety, pharmacokinetic, and/or pharmacodynamic profile in Part 1.
7. Two separate randomization schedules will be used. One for the sentinel group and one to complete enrollment of Part 2 subjects. Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure in the sentinel group are reviewed.
8. Efficacious and safe dose level(s) and regimen(s) with fixed duration of 3 months will be selected based on data from Part 1. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens.
9. Total monthly dose may be divided into weekly, bi-weekly (every 2 weeks), and/or monthly dosing, and total monthly dose will not exceed 480 mg. However, the total monthly SC dose of 480 mg will only be explored in a weekly or bi-weekly dosing regimen.
10. The sentinel group will consist of at least 1 active and 1 placebo subject per each dosing level and regimen. Subjects enrolled in the sentinel group are dosed and followed per the Time and Events Tables. Safety data from all subjects in the sentinel group will be reviewed (must be at least 2 weeks of expsosure, but may include more data).
11. An optional Japanese Part 2 sub-study is planned. The exact details may be found in a country-specific protocol amendment/supplement and will not be detailed here. The Japan sub-study may include more intensive PK monitoring and/or potential overnight/hospital stay.

Amended text:



1. ~~Hepatitis B virus e-antigen status of the subject population in Part 2 will depend on safety, pharmacokinetic, and/or pharmacodynamic profile in Part 1.~~ **HBeAg positive and negative subjects will be enrolled**
2. Two separate randomization schedules will be used. One for the sentinel group and one to complete enrollment of Part 2 subjects. Randomization for the remainder of subjects in Part 2 will continue after safety data from at least 2 weeks of exposure in the sentinel group are reviewed.
3. ~~Efficacious and safe dose level(s) and regimen(s) with fixed duration of 3 months will be selected based on data from Part 1. Part 2 may explore 2 or 3 different dose levels each at 2 different dosing regimens.~~
4. ~~Total monthly dose may be divided into weekly, bi-weekly (every 2 weeks), and/or monthly dosing, and total monthly dose will not exceed 480 mg. However, the total monthly SC dose of 480 mg will only be explored in a weekly or bi-weekly dosing regimen.~~

   ~~5.~~ **3.** The sentinel group will consist of at least 1 active and 1 placebo subject per each dosing level and regimen. Subjects enrolled in the sentinel group are dosed and followed per the Time and Events Tables. Safety data from all subjects in the sentinel group will be reviewed (must be at least 2 weeks of expsosure, but may include more data).

   ~~6.~~ **4. Matching placebo for each treatment arm (dose/regimen)**

   5. An optional Japanese Part 2 sub-study is planned. The exact details may be found in a country-specific protocol amendment/supplement and will not be detailed here. The Japan sub-study may include more intensive PK monitoring and/or potential overnight/hospital stay.

Section 4.2 Treatment Arms and Duration, Paragraph 4 and 5

Rationale: To update the treatments to be studied in Part 2 and to update text to include the optional additional 9 month follow-up period

Original text:

In Part 2, the total study duration, including screening, treatment and post-treatment follow-up, is not expected to exceed 29 weeks for each subject (Figure 4 to Figure 61GSK3389404 (≤480 mg total monthly dose) or placebo (Figure 2) at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly dosing regimen. Two or 3 dose levels each at 2 different dosing regimens will be explored.

For once weekly dosing (Figure 4), study treatment will be administered weekly and subjects followed weekly in outpatient visits until the final dose (Day 78) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 85, 92, 99, 113, 141, and 169.

Amended text:

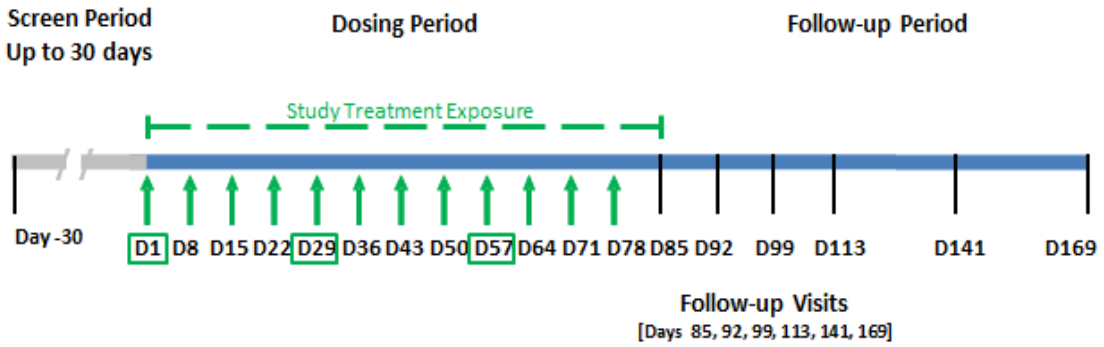
In Part 2, the total study duration, including screening, treatment and post-treatment follow-up, is not expected to exceed ~~29~~ **65** weeks for each subject (Figure 4 and ~~to Figure 6 GSK3389404 (≤480 mg total monthly dose) or placebo (Figure 2) at once weekly, bi-weekly (every 2 weeks), or monthly dosing regimens. However, the total monthly SC dose of 480 mg will only be explored in a once weekly or bi-weekly dosing regimen. Two or 3 dose levels each at 2 different dosing regimens will be explored.~~ Figure 5.

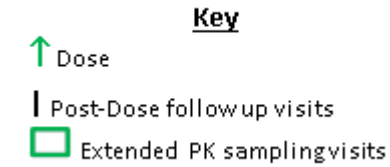
For once weekly dosing (Figure 4), study treatment will be administered weekly and subjects followed weekly in outpatient visits until the final dose (Day 78) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 85, 92, 99, 113, 141, and 169. **An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.**

Section 4.2 Treatment Arms and Duration, Figure 4

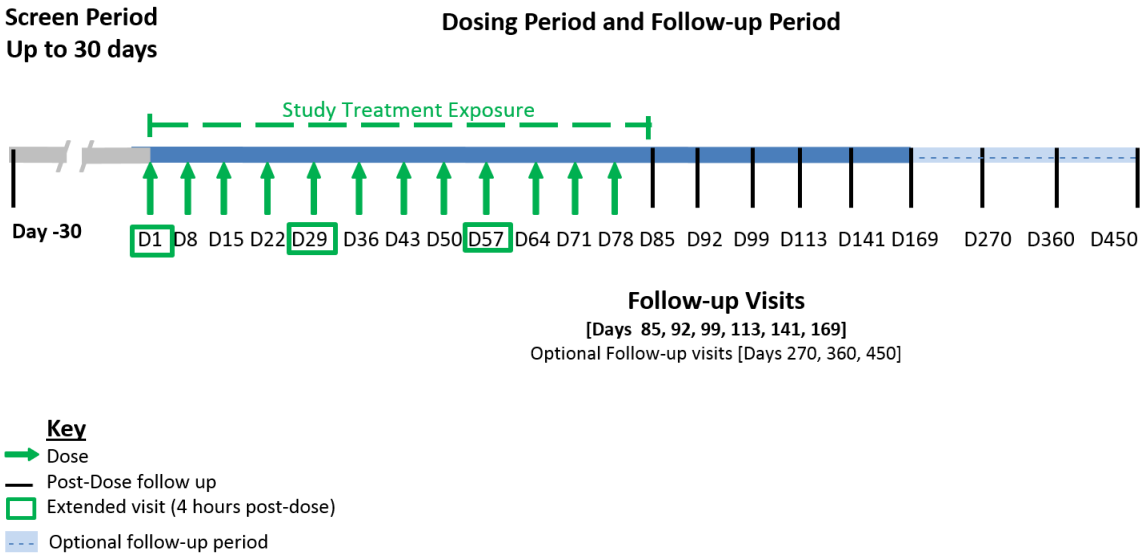
Rationale: To update the figure to include the optional additional follow-up period (please note that the figure was amended, but a 'strike-through' figure was not included in the amended text)

Original text:





Amended text:



Section 4.2 Treatment Arms and Duration, Paragraph 6

Rationale: To update the treatment and populations to be studied in Part 2

Original text:

For bi-weekly (every 2 weeks) dosing (Figure 5), study treatment will be administered every 2 weeks and subjects followed weekly in outpatient visits until the final dose (Day 71) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 78, 85, 92, 99, 113, 141, and 169.

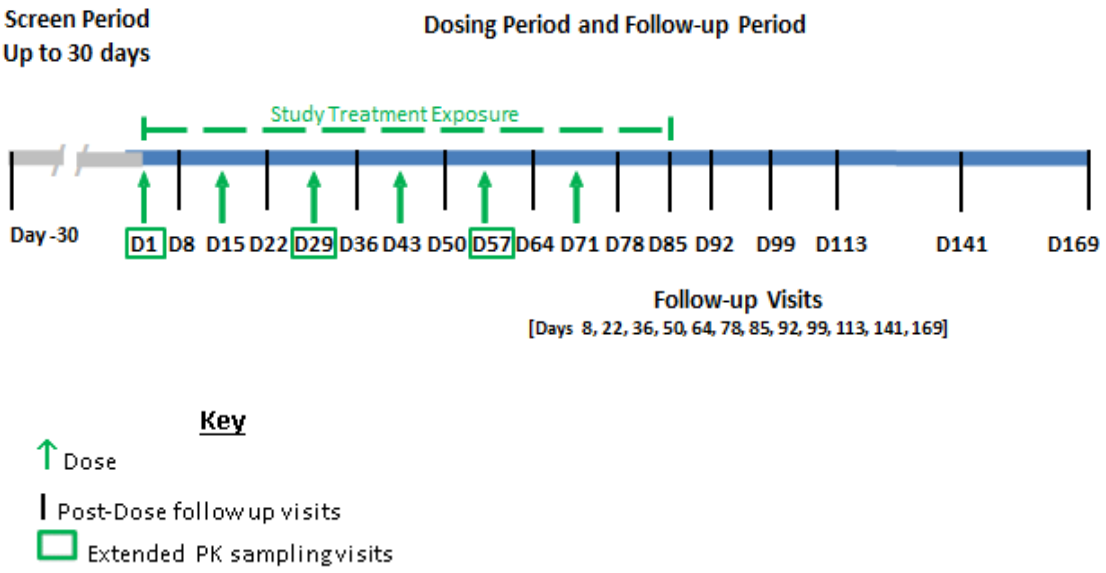
Amended text:

For bi-weekly (every 2 weeks) dosing (Figure 5), study treatment will be administered every 2 weeks and subjects followed weekly in outpatient visits until the final dose (Day 71) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 78, 85, 92, 99, 113, 141, and 169. **An optional extended post treatment follow-up period will be offered to subjects with study visits on Days 270, 360, and 450.**

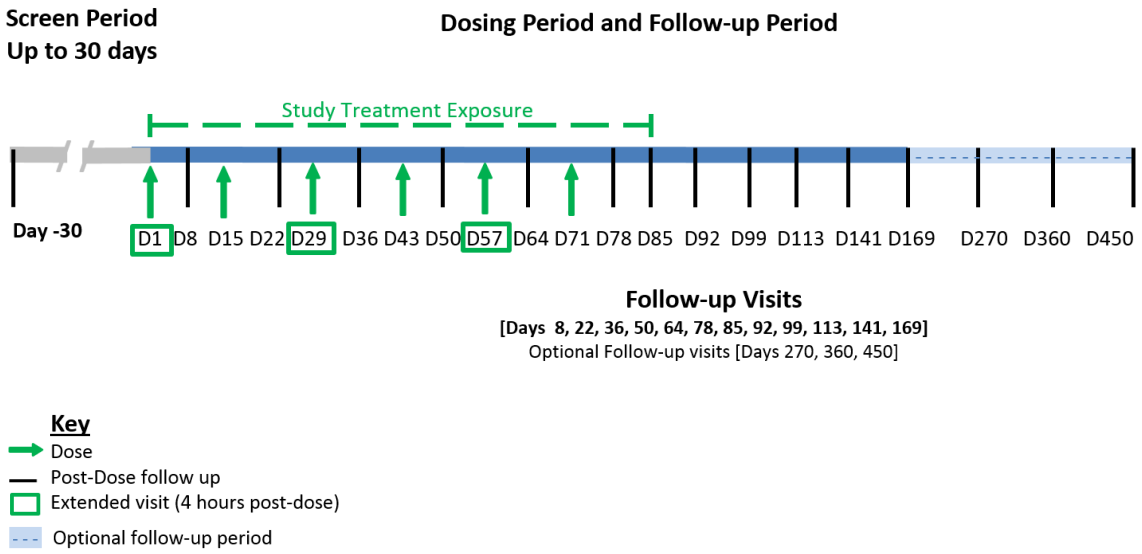
Section 4.2 Treatment Arms and Duration, Figure 5

Rationale: To update the figure to include the optional additional follow-up period (please note that the figure was amended, but a 'strike-through' figure was not included in the amended text)

Original text:



Amended text:



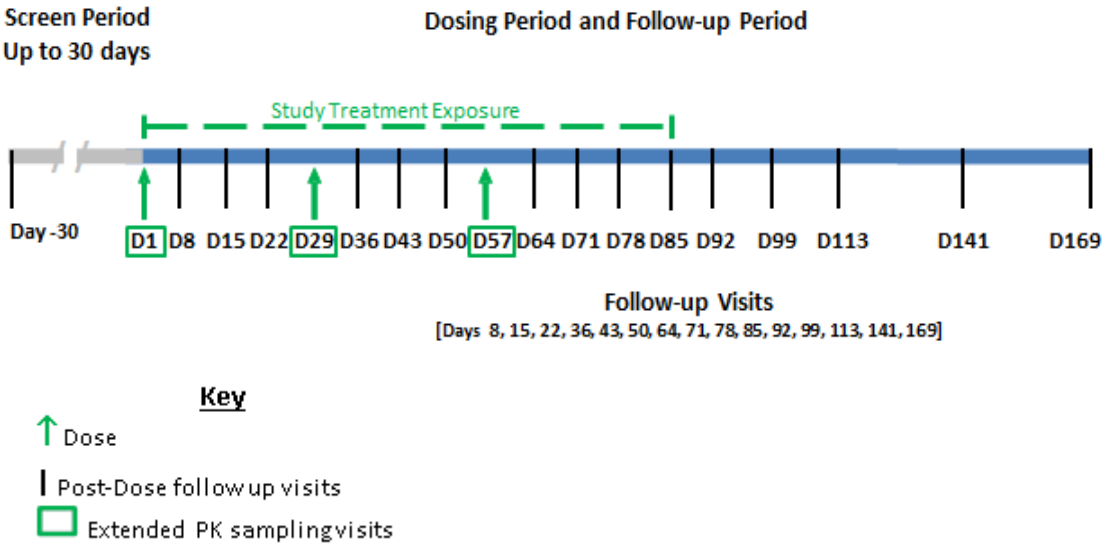
Section 4.2 Treatment Arms and Duration, Paragraph 7

Rationale: To update the treatments to be studied in Part 2. Since a monthly dose will not be included, the text and associating figure were removed (please note that the figure was removed, but a 'strike-through' figure was not included in the amended text)

Original text:

For once monthly dosing (Figure 6), study treatment will be administered monthly and subjects followed weekly in outpatient visits until the final dose (Day 57) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 64, 71, 78, 85, 92, 99, 113, 141, and 169.

Figure 6 Part 2 Multiple Dose, Dose-Ranging Participation Flow (Once Monthly Dosing)



Amended text:

~~For once monthly dosing (Figure 6), study treatment will be administered monthly and subjects followed weekly in outpatient visits until the final dose (Day 57) is administered. After the final dose, subjects will continue post-treatment follow-up in an outpatient setting on Days 64, 71, 78, 85, 92, 99, 113, 141, and 169.~~

Section 4.3 Type and Number of Subjects, Paragraph 1

Rationale: To update the treatment and populations to be studied in Part 2.

Original text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAgnegative- subjects. A decision will be made about the specific CHB population for enrollment in Part 2 after completion of dosing in Part 1 (after review of safety, tolerability, PD differences between HBeAg status).

Amended text:

Adult male and female subjects with CHB between 18 and 70 years of age, inclusive are planned for inclusion. Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects and Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAg negative- subjects. ~~A decision will be made about the specific CHB population for enrollment in Part 2 after completion of dosing in Part 1 (after review of safety, tolerability, PD differences between HBeAg status).~~ **For Part 2, both HBeAg-positive and HBeAg- negative subjects will be enrolled.**

Section 4.3 Type and Number of Subjects, Paragraph 2 and sub-bullets 1, 2, and 3

Rationale: To update the treatments to be studied in Part 2 and to provide update with preliminary clinical data from Part 1

Original text:

Approximately 150 subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, approximately 20 to 40 subjects with CHB are planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range is provided because different countries and sites may be enrolling under the older versions of the protocol.
- In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. The exact number of subjects to be enrolled will be data driven from Part 1 (e.g., safety, tolerability, PK, and PD effects) and will depend on the number of dose levels/regimens selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will ensure enough power for Part 2 with or without the optional Japanese Part 2 sub-study and allow for an approximate 14% overall drop-out rate, so that there are 10 evaluable subjects in each active treatment group and 12 subjects in placebo without the optional Japanese Part 2 sub-study for the primary analysis.
- If Japan participates in the optional Japanese Part 2 sub-study, approximately 30 subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement

Amended text:

Approximately ~~150~~ **73** subjects with CHB are planned for randomization to study treatment (GSK3389404 or placebo). This number assumes full enrolment in the optional Japanese sub-study.

- In Part 1, approximately 20 to 40 subjects with CHB ~~are~~ **were** planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range is provided because different countries and sites may be enrolling under the older versions of the protocol. **Twelve subjects were enrolled for part 1 and Part 1 has completed enrollment.**
- In Part 2, approximately ~~80~~**39** subjects with CHB are planned for randomization to study treatment. ~~The exact number of subjects to be enrolled will be data driven from Part 1 (e.g., safety, tolerability, PK, and PD effects) and will depend on the number of dose levels/regimens selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group).~~ Enrolling approximately ~~80~~ **39** subjects will ensure enough power for Part 2 with or without the optional Japanese Part 2 sub-study ~~and allow for an approximate 14% overall drop-out rate~~, so that there are **11~~0~~** subjects in each active treatment group and ~~12~~**6** subjects in placebo without the optional Japanese Part 2 sub-study for the primary analysis.
- If Japan participates in the optional Japanese Part 2 sub-study, approximately ~~30~~ **22** subjects may be enrolled. The exact number of subjects to be enrolled may be found in a Japanese-specific protocol amendment/supplement

Section 4.5 Dose Justification

Rationale: To provide updates of the pre-clinical data

Original text:

The GSK3389404 dosing regimens selected for this study were based on observed human PK parameters, in vivo antiviral exposure-response relationship, and predicted safety margins relative to the 13-week no observed adverse effect level (NOAEL), AUC and C_{max} in monkeys [ISIS Study Number 712408-AS02, 2016].

Amended text:

The GSK3389404 dosing regimens selected for this study were based on observed human PK parameters, in vivo antiviral exposure-response relationship, and predicted safety margins relative to the 13- **and 39-**week no observed adverse effect level (NOAEL), AUC and C_{max} in monkeys [ISIS Study Number 712408-AS02, 2016; **ISIS Study Number 712408-AS05, 2017**].

Section 4.5.1 Observed Human Pharmacokinetics

Rationale: To update with preliminary clinical data from Part 1 and to provide updates of the pre-clinical data

Original text:

GSK3389404 has been administered to healthy adult subjects in Study 202007as single SC doses at doses of 10 to 120 mg, or as repeated SC doses (once weekly for 4 weeks) at doses of 30 to 120 mg. Study 202007 was a Phase I, first time in human, randomized, double-blind, placebo-controlled, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404. At the time of this protocol amendment writing, Study 202007 has been completed, and the final study report is in progress. The human PK parameters are presented in Table 1. Based on PK data, GSK3389404 showed dose proportional- PK with a mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose. The observed human PK data were evaluated using noncompartmental analysis (NCA) in Phoenix WinNonlin- version 6.3. All ISIS50538 (GSK3228836) plasma concentrations were non-quantifiable.

Amended text:

GSK3389404 has been administered to healthy adult subjects in Study 202007 **and in CHB adult patients in Part 1 of this study (Study 205670).**

Study 202007 was a Phase I, first time in human, randomized, double-blind, placebo controlled-, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404. GSK3389404 was administered to healthy adult subjects as single SC doses at doses of 10 to 120 mg, or as repeated SC doses (once weekly for 4 weeks) at doses of 30 to 120 mg. ~~Study 202007 was a Phase I, first time in human, randomized, double-blind, placebo-controlled, dose escalation study to determine the safety, tolerability, and PK profile of GSK3389404.~~ At the time of this protocol amendment writing, ~~Study 202007 has been completed, and~~ the final study report for study 202007 **has been completed** ~~is in progress~~. The human PK parameters are presented in Table 1. Based on PK data, GSK3389404 showed dose proportional- PK with a mean half-life of approximately 4 to 5 hours at a dose range of 10 to 120 mg. GSK3389404 plasma concentrations were similar after the first and fourth weekly dose, indicating no accumulation in plasma concentration after multiple doses. Half-life and plasma exposure (AUC and C_{max}) of GSK3389404 following multiple doses were consistent with those observed following a single dose. The observed human PK data were evaluated using noncompartmental analysis (NCA) in Phoenix WinNonlin- version 6.3. All ISIS50538 (GSK3228836) plasma concentrations were ~~non-quantifiable.~~ **below the LLOQ of 10 ng/mL.**

In this study (Study 205670), GSK3389404 has been administered to CHB adult patients as single SC doses at doses of 30 mg and 120 mg. At the time of this protocol amendment writing, six CHB patients have been administered GSK3389404 (3 at 30 mg and 3 at 120 mg single dose). Based on the preliminary PK analysis, the mean

half-life was approximately 4 to 5 hours at the dose of 30 mg and 120 mg in CHB patients, consistent with that in healthy subjects. The observed human PK data were evaluated using noncompartmental analysis (NCA) in Phoenix WinNonlin-version 6.3.

Section 4.5.1 Observed Human Pharmacokinetics, Table 1

Rationale: To update with preliminary data from Part 1 and to provide updates of the pre-clinical data

Original text:

Summary of Selected Plasma GSK3389404 Pharmacokinetic Parameters in Human

Dose (mg)	**10**	**30**			**60**			**120**		
Cohort[1]	A	B	E	E	C	F	F	D	G	G
Day	1	1	1	22	1	1	22	1	1	22
N	6	5[2]	6	6	6	6	6	6	6	6
Half life[3] (hr)	3.8 (66)	3.7 (81)	3.0 (34)	4.1 (61)	5.1 (71)	5.0 (206)	3.1 (51)	4.1 (29)	3.7 (43)	3.4 (38)
T_{max}[4] (hr)	1 (1-4)	2 (1-2)	2 (1-4)	2 (1-4)	3 (1-4)	2 (2-2)	2 (1.5-4)	4 (3-4)	2 (1.5-4)	2 (2-4)
C_{max}[3] (ng/mL)	90 (24)	295 (69)	228 (32)	194 (20)	512 (57)	692 (35)	577 (43)	803 (49)	1167 (50)	1107 (55)
$AUC_{(0-\infty)}$[3] (ng*hr/mL)	614 (27)	1969 (35)	1394 (24)	1526 (34)	4578 (30)	5875 (52)	3966 (23)	7718 (35)	8039 (36)	8640 (32)
Fold coverage C_{max}[5]	642	197	255	298	113	84	100	72	50	52
Fold coverage AUC[5]	759	237	334	305	102	79	117	60	58	54

7. Cohort A – D were single dose cohorts. Cohort E – G were multiple dose cohorts (weekly dose for 4 weeks).
8. In Cohort B (30-mg single) dose, the pharmacokinetic profile in one subject was atypical and not evaluable.
9. Data are presented as geometric mean (geometric coefficient of variation %).
10. Data are presented as Median (range).
11. Fold coverage based on monkey NOAEL (no observed adverse effect level): NOAEL C_{max} = 57.9 μg/mL and NOAEL $AUC_{(0-\infty)}$ = 465.7 μg•h/mL at 30 mg/kg/week.

Amended text:

Summary of Selected Plasma GSK3389404 Pharmacokinetic Parameters in ~~Humans~~ **Healthy Adult Subjects**

Dose (mg)	**10**	**30**			**60**			**120**		
Cohort[1]	A	B	E	E	C	F	F	D	G	G

Day	1	1	1	22	1	1	22	1	1	22
N	6	5[2]	6	6	6	6	6	6	6	6
Half life[3] (hr)	3.8 (66)	3.7 (81)	3.0 (34)	4.1 (61)	5.1 (71)	5.0 (206)	3.1 (51)	4.1 (29)	3.7 (43)	3.4 (38)
T_{max}[4] (hr)	1 (1-4)	2 (1-2)	2 (1-4)	2 (1-4)	3 (1-4)	2 (2-2)	2 (1.5-4)	4 (3-4)	2 (1.5-4)	2 (2-4)
C_{max}[3] (ng/mL)	90 (24)	295 (69)	228 (32)	194 (20)	512 (57)	692 (35)	577 (43)	803 (49)	1167 (50)	1107 (55)
$AUC_{(0-\infty)}$[3] (ng*hr/mL)	614 (27)	1969 (35)	1394 (24)	1526 (34)	4578 (30)	5875 (52)	3966 (23)	7718 (35)	8039 (36)	8640 (32)
Fold coverage C_{max}[5]	~~642~~ **586**	~~197~~ **179**	~~255~~ **231**	~~298~~ **273**	~~113~~ **103**	~~84~~ **76**	~~100~~ **91**	~~72~~ **66**	~~50~~ **45**	~~52~~ **48**
Fold coverage AUC[5]	~~759~~ **802**	~~237~~ **250**	~~334~~ **353**	~~305~~ **323**	~~102~~ **108**	~~79~~ **84**	~~117~~ **124**	~~60~~ **64**	~~58~~ **61**	~~54~~ **57**
Fold coverage C_{max}[6]	**32**	**10**	**13**	**15**	**6**	**4**	**5**	**4**	**2**	**3**
Fold coverage AUC[6]	22	7	10	9	3	2	3	2	2	2

1. Cohort A – D were single dose cohorts. Cohort E – G were multiple dose cohorts (weekly dose for 4 weeks).
2. In Cohort B (30-mg single) dose, the pharmacokinetic profile in one subject was atypical and not evaluable.
3. Data are presented as geometric mean (geometric coefficient of variation %).
4. Data are presented as Median (range).
5. Fold coverage based on **exposure (AUC and Cmax) at** ~~monkey~~ NOAEL (no observed adverse effect level) **of 13-week monkey study**: Gender averaged C_{max} = ~~57.9~~ **52.7** μg/mL and **gender averaged** $AUC_{(0-\infty)}$ = ~~465.7~~ **492.7** μg•h/mL at **NOAEL of** 30 mg/kg/week.
6. **Fold coverage based on exposure (AUC and Cmax) at NOAEL (no observed adverse effect level) of 39-week monkey study: Gender averaged C_{max} = 2.9 μg/mL and gender averaged $AUC_{(0-\infty)}$ = 13.5 μg•h/mL at NOAEL of 2 mg/kg/week.**

Section 4.5.2 Safety Margin Calculations, Paragraph 1

Rationale: To provide updates of the pre-clinical data

Original text:

From the 13-week toxicology studies in mice and monkeys, the NOAELs were identified at 2 and 30 mg/kg/week, respectively [ISIS Study Number 712408-AS01, 2016; ISIS Study Number 712408-AS02, 2016].

Amended text:

From the 13-week toxicology studies in mice and monkeys, the NOAELs were identified at 2 and 30 mg/kg/week, respectively [ISIS Study Number 712408-AS01, 2016; ISIS Study Number 712408-AS02, 2016]. **The NOAELs of 26-week rabbit and 39-week**

monkey studies were 6 and 2 mg/kg/week, respectively [ISIS Study Number 712408-AS04, 2017; ISIS Study Number 712408-AS05, 2017].2

Section 4.5.2 Safety Margin Calculations, Paragraph 2

Rationale: To provide updates of the pre-clinical data

Original text:

Based on observed PK data in healthy adult subjects (Study 202007), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is at least 50-fold lower than the monkey NOAEL C_{max} and AUC, respectively (Table 1).

Amended text:

Based on observed PK data in healthy adult subjects (Study 202007), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is at least **45**~~50~~-fold lower than the ~~monkey~~ NOAEL C_{max} and AUC **values at NOAEL of 13-week monkey study, and at least 2-fold lower than the C_{max} and AUC values at NOAEL of 39-week monkey study** respectively (Table 1). **Based on the preliminary PK analysis in Part 1 of this study (Study 205670), C_{max} and AUC of GSK3389404 at the highest dose tested (120 mg) is lower than the C_{max} and AUC values at NOAEL of 13-week and 39-week monkey study**.

Section 4.5.2 Safety Margin Calculations, Paragraph 4 and 5

Rationale: To provide updates of the pre-clinical data

Original text:

Table 2 shows the observed and predicted human GSK3389404 PK, the predicted liver concentrations, and the fold safety margins of the predicted exposures after single, SC administration of GSK3389404 relative to the 13-week monkey NOAEL. In addition, liver concentration fold coverage based on the estimated human liver concentration of ISIS 505358 (parent) from a previously completed Phase I clinical trial is presented.

In addition, Bayesian predictive probabilities of $AUC_{(0-\infty)}$ and C_{max} less than the respective mean monkey NOAEL were calculated for the 240 mg dose level using a power model and using observed data at 10, 30, 60 and 120 mg dose levels from Study 202007. The predictive probability of $AUC_{(0-\infty)}$ and C_{max} crossing the respective threshold values of mean monkey NOAEL are very low (<0.01%) and are within the acceptable range (i.e. <50%) for the 240 mg treatment group.

Amended text:

Table 2 shows the observed and predicted human GSK3389404 PK, the predicted liver concentrations, and the fold safety margins of the predicted exposures after single, SC

administration of GSK3389404 relative to the 13- **and 39-**week monkey NOAEL. In addition, liver concentration fold coverage based on the estimated human liver concentration of ISIS 505358 (parent) from a previously completed Phase I clinical trial is presented.

In addition, Bayesian predictive probabilities of $AUC_{(0-\infty)}$ and C_{max} less than the respective ~~mean~~ **13-week** monkey **study mean** NOAEL were calculated for the 240 mg dose level using a power model and using observed data at 10, 30, 60 and 120 mg dose levels from Study 202007. The predictive probability of $AUC_{(0-\infty)}$ and C_{max} crossing the respective threshold values of ~~mean~~ **13-week** monkey **study mean** NOAEL are very low (<0.01%) and are within the acceptable range (i.e. <50%) for the 240 mg treatment group.

Section 4.5.2 Safety Margin Calculations, Table 2 and footnotes

Rationale: To provide updates of the pre-clinical data

Original text:

Human Dose (mg)	Observed GSK3389404 Plasma C_{max} (ng/mL)[1]	Observed GSK3389404 Plasma AUC (h•ng/mL)[1]	Predicted Parent Liver Concentration (μg/g)[2]	Fold Coverage Plasma C_{max}[3]	Fold Coverage Plasma AUC[3]	Fold Coverage Of Estimated Human Liver Concentration from Phase I Parent Study[4]
10	90	614	2.8	642	759	161
30	295	1968	8.2	197	237	55
60	512	4578	16.2	113	102	28
120	803	7718	31.4	72	60	14
240	1728[5]	15992[5]	59.0	34	29	8

NOAEL = no observed adverse effect level

7. Geometric mean of GSK3389404 plasma human PK observed at 10 to 120 mg in Study 202007 and predicted for 240 mg.
8. Liver concentration in monkeys at 1 week after a single dose was approximately 20% of that at 13 weeks (steady state) after repeated once weekly doses. Human steady state liver concentration of parent compound (ISIS 505358) was estimated based on 13-week monkey liver tissue concentration and assumed to be 20% that of steady state. Liver concentration was fit to an E_{max} model and then extrapolated.
9. Fold coverage based on monkey NOAEL; GSK3389404 plasma C_{max} = 57.9 μg/mL and plasma $AUC_{(0-\infty)}$ = 465.7 μg•h/mL at 30 mg/kg/week.
10. At 450 mg of ISIS 505358 (the highest dose tested in ISIS 505358 first time in human study), human liver concentration (4 weeks) = 450 μg/g, based on allometric scaling [Geary, 2009]. Fold coverage = 450 μg/g divided by the predicted liver concentration.
11. Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (10 to 120 mg) given dose proportionality.

Amended text:

Human Dose (mg)	Observed GSK3389404 Plasma C_{max} (ng/mL)[1]	Observed GSK3389404 Plasma AUC (h•ng/mL)[1]	Predicted Parent Liver Concentration (μg/g)[2]	Fold Coverage Plasma Based on 13-week monkey study NOAEL		Fold Coverage Plasma Based on 39-week monkey study NOAEL		Fold Coverage Of Estimated Human Liver Concentration from Phase I Parent Study[4,5]
				C_{max}	AUC	C_{max}	AUC	
10	90	614	2.8	~~642~~**586**	~~759~~**802**	**32**	**22**	161
30	295	1968	8.2	~~197~~**179**	~~237~~**250**	**10**	**7**	55
60	512	4578	16.2	~~113~~**103**	~~102~~**108**	**6**	**3**	28
120	803	7718	31.4	~~72~~**66**	~~60~~**64**	**4**	**2**	14
240	1728[6,5]	15992[6,5]	59.0	~~34~~**30**	~~29~~**31**	**2**	**0.8**	8

NOAEL = no observed adverse effect level

1. Geometric mean of GSK3389404 plasma human PK observed at 10 to 120 mg in Study 202007 and predicted for 240 mg.
2. Liver concentration in monkeys at 1 week after a single dose was approximately 20% of that at 13 weeks (steady state) after repeated once weekly doses. Human steady state liver concentration of parent compound (ISIS 505358) was estimated based on 13-week monkey liver tissue concentration and assumed to be 20% that of steady state. Liver concentration was fit to an E_{max} model and then extrapolated.
3. Fold coverage based on **13-week** monkey **study** NOAEL; GSK3389404 **gender averaged** plasma C_{max} =~~57.9~~ **52.7** μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = ~~465.7~~**492.7** μg•h/mL at 30 mg/kg/week.
4. **Fold coverage based on 39-week monkey study NOAEL; GSK3389404 gender averaged plasma C_{max} = 2.9 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 13.5 μg•h/mL at 2 mg/kg/week.**
   ~~4.~~ **5.** At 450 mg of ISIS 505358 (the highest dose tested in ISIS 505358 first time in human study), human liver concentration (4 weeks) = 450 μg/g, based on allometric scaling [Geary, 2009]. Fold coverage = 450 μg/g divided by the predicted liver concentration.
   ~~5.~~ **6.** Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (10 to 120 mg) given dose proportionality.

Section 4.5.3 In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, second paragraph

Original text:

ISIS 505358 is the parent compound of the prodrug GSK3389404, and has not been administered to HBV infected patients. Therefore, no direct antiviral activity data with ISIS 505358 from humans are available for extrapolation. To establish an exposureresponse- relationship, an in vivo efficacy study of GSK3389404 dosed once weekly for 4 weeks and ASO's liver tissue concentrations were measured in HBV transgenic mice.

Amended text:

ISIS 505358 is the parent compound of the prodrug GSK3389404, and ~~has not been administered to~~ **is currently being studied in** HBV infected patients. Therefore, no direct antiviral activity data with ISIS 505358 from humans are available for

extrapolation. To establish an exposure-response relationship, an in vivo efficacy study of GSK3389404 dosed once weekly for 4 weeks and ASO's liver tissue concentrations were measured in HBV transgenic mice.

Section 4.5.3 In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, fifth paragraph

Rationale: to update with treatments that will be studied in Part 2, total monthly doses will not be explored

Original text:

Thus, a total monthly dose not exceeding 480 mg GSK3389404 (weekly doses of 120 mg or bi-weekly doses of 240 mg) may be selected for Part 2.

Amended text:

~~Thus, a total monthly dose not exceeding 480 mg GSK3389404 (weekly doses of 120 mg or bi-weekly doses of 240 mg) may be selected for Part 2.~~

Section 4.5.3 In vivo Exposure-Response Relationship of GalNAc Conjugated and Unconjugated Compounds, Table 3

Rationale: To provide updates of the pre-clinical data

Original text:

Human Total Monthly Dose (mg)	**Human Repeat Dose (mg)[1]**	**Observed GSK3389404 Plasma C_{max} (ng/mL)[2]**	**Observed GSK3389404 Plasma AUC (h•ng/mL)[2]**	**Predicted Parent Liver Concentration at Week 13 (μg/g)[3]**	**Observed Fold Coverage Plasma C_{max}[4]**	**Observed Fold Coverage Plasma AUC[4]**	**Fold Coverage of Predicted Human Liver Concentration at Week 13[5]**
120	30 QW	194	1526	41	298	305	34
240	60 QW	577	3966	81	100	117	17
480	120 QW	1107	8640	157	52	54	9
480	240 Q2W	2200	16769	157	26	28	9

NOAEL = no observed adverse effect level

7. QW: dose every week. Q2W: dose every 2 weeks.

8. Geometric mean of GSK3389404 plasma human PK observed following repeat weekly SC dose of 30 to 120 mg for 4 weeks in Study 202007. The values for 240 mg were predicted
9. Human liver concentration of parent compound (ISIS 505358) at Week 13 was estimated based on 13-week monkey liver tissue concentration (an average of 1404 μg/g at 30 mg/kg/week for 13 weeks). Liver concentration was fit to E_{max} model and then extrapolated.
10. Fold coverage based on monkey NOAEL (30 mg/kg/week for 13 weeks): plasma GSK3389404 C_{max} = 57.9 μg/mL and plasma $AUC_{(0-\infty)}$ = 465.75 μg•h/mL. Liver tissue concentration of parent compound (ISIS 505358) = 1404 μg/g.

Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (30 to 120 mg) given dose proportionality

Amended text:

Human Total Monthly Dose (mg)	**Human Repeat Dose (mg)[1]**	**Observed GSK3389404 Plasma**		**Predicted Parent Liver Concentration at Week 13 (μg/g)[3]**	**Observed Fold Coverage**		**Fold Coverage of Predicted Human Liver Concentration at Week 13[6]**	**Observed Fold Coverage**		**Fold Coverage of Predicted Human Liver Concentration at Week 13[6]**
		C_{max} (ng/mL)[2]	**AUC (h•ng/mL)[2]**		**Plasma C_{max}[4]**	**Plasma AUC[4]**		**Plasma C_{max}[5]**	**Plasma AUC[5]**	
120	30 QW	194	1526	41	272	323	34	15	9	4
240	60 QW	577	3966	81	91	124	17	5	3	2
480	120 QW	1107	8640	157	48	57	9	3	2	1
480	240 Q2W	2200	16769	157	24	29	9	1	0.8	1

NOAEL = no observed adverse effect level

1. QW: dose every week. Q2W: dose every 2 weeks.
2. Geometric mean of GSK3389404 plasma human PK observed following repeat weekly SC dose of 30 to 120 mg for 4 weeks in Study 202007. The values for 240 mg were predicted
3. Human liver concentration of parent compound (ISIS 505358) at Week 13 was estimated based on 13-week monkey liver tissue concentration (an average of 1404 μg/g at 30 mg/kg/week for 13 weeks). Liver concentration was fit to E_{max} model and then extrapolated.
4. Fold coverage based on **13-week** monkey **study** NOAEL (30 mg/kg/week ~~for 13 weeks~~): **gender averaged** plasma GSK3389404 C_{max} = ~~57.9~~**52.7** μg/mL and plasma $AUC_{(0-\infty)}$ = ~~465.75~~ **492.7** μg•h/mL. **Gender averaged l**~~L~~iver tissue concentration of parent compound (ISIS 505358) = 1404 μg/g.
5. **Fold coverage based on 39-week monkey study NOAEL (2 mg/kg/week): gender averaged plasma GSK3389404 C_{max} = 2.9 μg/mL and gender averaged plasma $AUC_{(0-\infty)}$ = 13.5 μg•h/mL. Gender averaged liver tissue concentration of parent compound (ISIS 505358) = 176 μg/g.**
6. Predicted using linear regression (zero intercept) based on observed human PK data from previous dose cohorts (30 to 120 mg) given dose proportionality

Section 4.5.4 Dose Escalation Justification, Paragraph 1

Rationale: To provide updates of the pre-clinical data

Original text:

The planned GSK3389404 doses for this study are 30, 60, 120 and 240 mg administered by SC injection for the single dose cohorts (Part 1). The proposed doses of GSK3389404 may be adjusted during the course of the study as the safety, PK, and PD results are reviewed. Doses in Part 2 will be selected such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma C_{max} and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time ($AUC_{(0-\infty)}$) observed at the NOAEL dose of 30 mg/kg/day in the 13-week monkey toxicity study (C_{max} = 57.9 μg/mL; $AUC_{(0-\infty)}$ = 465.75 μg•h/mL). Escalation to the next higher single dose or to Part 2 will only proceed after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and the investigator at the Dose Escalation Committee meeting (Section 10.8.1) and determined to be safe, tolerable, and supportive of escalation.

Amended text:

The planned GSK3389404 doses for this study are 30, 60, 120 and 240 mg administered by SC injection for the single dose cohorts (Part 1). The proposed doses of GSK3389404 may be adjusted during the course of the study as the safety, PK, and PD results are reviewed. Doses in Part 2 will be selected such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma C_{max} and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time ($AUC_{(0-\infty)}$) observed at

- the NOAEL ~~dose~~ of 30 mg/kg/day in the 13-week monkey toxicity study (C_{max} = ~~57.9~~ **52.7** μg/mL; $AUC_{(0-\infty)}$ = ~~465.75~~ **492.7**μg•h/mL) **and**
- **the NOAEL of 2 mg/kg/day in the 39-week monkey toxicity study (C_{max} = 2.9 μg/mL; $AUC_{(0-\infty)}$ = 13.5 μg•h/mL).**

Escalation to the next higher single dose or to Part 2 will only proceed after the PK, safety, and tolerability of the previous single dose level(s) are thoroughly reviewed by the study team and the investigator at the Dose Escalation Committee meeting (Section 10.8.1) and determined to be safe, tolerable, and supportive of escalation.

Section 4.6.1 Risk Assessment, Table 4, Liver Effects, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Liver Effects: In the 13-week GSK3389404 mouse study, doses ≥6 mg/kg/week caused increases in liver enzymes (9.4 X AST, 7.5 X ALT, 1.6 X ALP and/or 1.7 X bilirubin) with correlating histopathology changes which include minimal to mild hepatocellular hypertrophy, vacuolated macrophages and scattered single cell hepatocyte necrosis with evidence of reversibility following the 13-week recovery period. The mean liver concentration (13 μg/g) at the NOAEL of 2 mg/kg/week in the mouse is approximately 0.4- to 2.3-fold higher than the predicted clinical efficacious liver concentration range (EC_{90}-EC_{99}: 5.9 to 33 μg/g). The 42 to 238-fold higher liver concentrations (gender averages 1403 μg/g) were achieved at the NOAEL of 30 mg/kg/week in the 13-week monkey study.

In the ISIS 505358-CS1 Phase I study in healthy subjects, modest (1.03 to 1.41 X ULN) elevations in ALT that were transient and not associated with concurrent symptoms or increases in bilirubin were observed. All subjects with elevated ALT returned to baseline during post-treatment follow-up.

Amended text:

Liver Effects: In the 13-week GSK3389404 mouse study, doses ≥6 mg/kg/week caused increases in liver enzymes (9.4 X AST, 7.5 X ALT, 1.6 X ALP and/or 1.7 X bilirubin) with correlating histopathology changes which include minimal to mild hepatocellular hypertrophy, vacuolated macrophages and scattered single cell hepatocyte necrosis with evidence of reversibility following the 13-week recovery period. The mean liver concentration (13**.5** μg/g) at the NOAEL of 2 mg/kg/week in the mouse is approximately 0.4- to 2.3-fold higher than the predicted clinical efficacious liver concentration range (EC_{90}-EC_{99}: 5.9 to 33 μg/g). **In the 26-week mouse study, liver findings (eosinophilic hepatocytes, individual hepatocyte necrosis, presence of macrophages with vacuolated/granular cytoplasm (sinusoidal macrophages) and/or accumulations of pigmented macrophases and karyomegaly) without clinical chemistry correlates were not considered adverse. Liver concentration of ISIS 505358 (97.8 μg/g) at the NOAEL of 6 mg/kg/week in male mice was 16.6- to 3.0-fold of predicted clinical efficacious liver concentrations (EC_{90}-EC_{99}: 5.9 to 33 μg/g).** The 42 to 238-fold higher liver concentrations (gender averages 1403 μg/g) were achieved at the NOAEL of 30 mg/kg/week in the 13-week monkey study**. In the 39-week monkey study, the liver concentration of ISIS 505358 (176 μg/g) at the NOAEL of 2 mg/kg/week was approximately 29.8- to 5.3-fold of predicted clinical efficacious liver concentration (EC_{90}-EC_{99}: 5.9 to 33 μg/g).**

Section 4.6.1 Risk Assessment, Table 4, Coagulation Effects, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Coagulation Effects: In the 13-week GSK3389404 monkey study, acute and transient test article-related changes in the coagulation included slightly prolonged (up to 4.2 seconds higher than the baseline value) aPTT values at 30 mg/kg/week. The prolongation was observed 4 hours after dosing on Days 1 and 91 and generally returned to baseline by 24 hours post-dose. These results are consistent with the aPTT results from the clinical and nonclinical studies of other phosphorothioate and MOE-modified phosphorothioate ASOs [Dorr, 2001; Levin, 2001; Henry, 2008; Kwoh, 2008].
In the ISIS 505358-CS1 Phase I study in healthy subjects, aPTT prolongations were observed at 3 to 5 hours post injection of ISIS 505358. The magnitudes of this prolongation were modest, not clinically significant and generally resolved within 12 to 24 hours after dosing.

Amended text:

Coagulation Effects: In the 13-week GSK3389404 monkey study, acute and transient test article-related changes in the coagulation included slightly prolonged (up to ~~4.2~~ **5.1** seconds higher than the baseline value) aPTT values at 30 mg/kg/week. The prolongation was observed 4 hours after dosing on Days 1 and 91 and generally returned to baseline by 24 hours post-dose. These results are consistent with the aPTT results from the clinical and nonclinical studies of other phosphorothioate and MOE-modified phosphorothioate ASOs [Dorr, 2001; Levin, 2001; Henry, 2008; Kwoh, 2008]. There was no test article-related coagulation prolongation in monkeys treated with GSK3389404 at doses up to 8 mg/kg/week for 39 weeks.
In the ISIS 505358-CS1 Phase I study in healthy subjects, aPTT prolongations were observed at 3 to 5 hours post injection of ISIS 505358. The magnitudes of this prolongation were modest, not clinically significant and generally resolved within 12 to 24 hours after dosing. **There was no test article-related coagulation prolongation in monkeys treated with GSK3389404 at doses up to 8 mg/kg/week for 39 weeks.**

Section 4.6.1 Risk Assessment, Table 4, Complement Activation, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Complement Activation: In the monkey GSK3389404 13-week study, minimal decreases in (up to 21% from baseline) C3 and increased complement fragment Bb (up to 3.6-fold over baseline) were observed in the 8 and 30 mg/kg groups, suggesting mild activation of the alternative complement pathway. The significance of these findings remains unclear because there was also an 11% decrease in C3 observed in male controls. These changes in aPTT, C3, Bb, ALT, and IgM were not seen during the 13-week recovery period.

Amended text:

Complement Activation: In the monkey GSK3389404 13-week study, minimal decreases in (up to 21% from baseline) C3 and increased complement fragment Bb (up to 3.6-fold over baseline) were observed in the 8 and 30 mg/kg groups, suggesting mild activation of the alternative complement pathway. The significance of these findings remains unclear because there was also an 11% decrease in C3 observed in male controls. These changes in aPTT, C3, Bb, ALT, and IgM were not seen during the 13-week recovery period. **In the 39-week monkey study, there was a mild and transient increase in complement fragment Bb (up to 2.1-fold over baseline compared to up to 1.4-fold over baseline in control) and decrease in C3 concentrations in individual animals at ≥ 0.5 mg/kg/week. These changes were not considered adverse since they were mild and transient.**

Section 4.6.1 Risk Assessment, Table 4, Pro-inflammatory effects/Constitutional or flu-like symptoms, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Pro-inflammatory Effects/Constitutional or Flu-Like Symptoms: At doses of ≥2 mg/kg/week GSK3889404 in the 13-week mouse study, vacuolated macrophages and mixed cell leucocytes were increased in incidence and/or magnitude at the site of injection compared to controls. However, this finding is considered to reflect the sensitivity of rodents to proinflammatory effects of ASOs [Henry, 2008] and evidence of reversibility was seen in the recovery interval. There were no significant injection site findings in the 13-week monkey study up to 30 mg/kg/week.

Amended text:

Pro-inflammatory Effects/Constitutional or Flu-Like Symptoms: At doses of ≥2 mg/kg/week GSK3889404 in the 13-week mouse study, vacuolated macrophages and mixed cell leucocytes were increased in incidence and/or magnitude at the site of injection compared to controls. . **In the 26-week mouse study, minimal to mild vacuolated/granular macrophages and increased incidence of mixed leukocytes were noted at the injection sites and/or non-injected skin sections in both sexes at doses of ≥0.5 mg/kg/week.** However, ~~this~~ **these** finding**s** ~~is~~**are** considered to reflect the sensitivity of rodents to proinflammatory effects of ASOs [Henry, 2008] and evidence of reversibility was seen in the recovery interval. There were no significant injection site findings in the 13-**and 39-**week monkey ~~study~~ **studies at doses** up to 30 **and 8** mg/kg/week, **respesctively**.

Section 4.6.1 Risk Assessment, Table 4, Kidney Effects, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Kidney Effects: No adverse kidney findings were observed in the mouse (up to 24 mg/kg/week) and monkey (up to 30 mg/kg/week) 13-week GSK3389404 studies. The presence of basophilic granules in the tubular epithelium in both species are considered indicative of cellular uptake of oligonucleotides and not considered adverse [Henry, 2000]. Following the 13-week recovery period, monkeys dosed with 30 mg/kg/week showed reversal of the basophilic granularity of proximal tubular epithelial cells of the kidney.

In humans administered 2'-MOE ASOs, no trends in laboratory parameters have been identified that suggested an effect on renal function.

Amended text:

Kidney Effects: No adverse kidney findings were observed in the mouse (up to 24 mg/kg/week) and monkey (up to 30 mg/kg/week) 13-week GSK3389404 studies **and in mice (up to 6 mg/kg/week) and monkeys (up to 8 mg/kg/week) following 26 and 39 weeks of repeat dosing, respectively.**The presence of basophilic granules in the tubular epithelium in both species **and occasionally vacuolated/granular macrophages surrounding the pelvic region of kidneys in mice** are considered indicative of cellular uptake of oligonucleotides **These findings were generally reversible by the end of recovery period, and therefore, were** not considered adverse [Henry, 2000]. ~~Following the 13-week recovery period, monkeys dosed with 30 mg/kg/week showed reversal of the basophilic granularity of proximal tubular epithelial cells of the kidney.~~

In humans administered 2'-MOE ASOs, no trends in laboratory parameters of kidney function have been identified that suggested an effect on renal function.

Section 4.6.1 Risk Assessment, Table 4, Kidney Effects, Strategy- Monitoring/Stopping Criteria

Rationale: To provide updates of the pre-clinical data

Original text:

Following confirmation of the criteria above, further evaluation may include but not be limited to 24-hour urine for analysis, consultation with a nephrology specialist, renal ultrasound, urine microscopy, serum creatinine kinase, SPEP/UPEP, and/or complement panel (C3, C4, C5a and Bb).

Amended text:

Following confirmation of the criteria above, further evaluation may include but not be limited to 24-hour urine for analysis, consultation with a nephrology specialist, renal ultrasound, urine microscopy, serum creatinine ~~kinase~~, SPEP/UPEP, and/or complement panel (C3, C4, C5a and Bb).

Section 4.6.1 Risk Assessment, Table 4, Decreased hematological parameters, Potential Risk/Summary of Data

Rationale: To provide updates of the pre-clinical data

Original text:

Decreased hematological parameters: No significant test article related changes in platelets were observed in the 13-week GSK3389404 mouse or monkey toxicity studies.

Amended text:

Decreased hematological parameters: No significant test article related changes in platelets were observed in the 13-week GSK3389404 mouse or monkey toxicity studies. I**n the 39-week monkey study, a marked and transient decrease in platelet count was noted in one male monkey administered GSK3389404 at 8 mg/kg/week on Day 184. The platelet count in this monkey returned to near baseline values by Day 191, despite continued treatment with test article. No significant test article-related changes in platelets were observed in the 26-week mouse study.**

In the 39-week monkey study, one high dose male had severe non-regenerative and potentially haemolytic anemia characterized by decreased red blood cell parameters and accompanied by decreased neutrophil counts, inflammation, renal injury/proteinuria, complement activation, metabolic acidosis, and decreased nutrient uptake. This animal was sacrificed on Day 218 (Week 32). Since non-regenerative anemia and other associated findings were only noted in this one animal, and have not been noted in other studies with antisense oligonucleotide therapies, even when accompanied by complement activation and/or proteinuria, the relationship of anemia to treatment in this case is unclear.

Section 4.6.2 Benefit Risk Summary, bullet point 3

Rationale: To provide updates of the pre-clinical data

Original text:

3. In Part 1, dose escalation will be stopped or a smaller dose increment selected when the predicted mean $AUC_{(0-\infty)}$ and C_{max} of the next dose level are expected to exceed the NOAEL exposures observed in the monkey toxicity study (Section 6.3).

Amended text:

1. In Part 1, dose escalation will be stopped or a smaller dose increment selected when the predicted mean $AUC_{(0-\infty)}$ and C_{max} of the next dose level are expected to exceed the NOAEL exposures observed in the **13-week** monkey toxicity study (Section 6.3).

Section 4.6.2 Benefit Risk Summary, bullet point 7

Rationale: To include text on an optional 9-month off treatment follow up period

Original text:

7. In Part 2, subjects are seen at the clinic on a weekly basis and safety assessments (AE/serious adverse event [SAE] review, physical exam, vital signs, ECG assessments) and comprehensive laboratory testing subjects is performed on a weekly or bi-weekly (every 2 weeks) basis. At the end of the 3-month treatment exposure period, subjects have extended follow-up to 12 weeks to assess safety.

Amended text:

7. In Part 2, subjects are seen at the clinic on a weekly basis and safety assessments (AE/serious adverse event [SAE] review, physical exam, vital signs, ECG assessments) and comprehensive laboratory testing subjects is performed on a weekly or bi-weekly (every 2 weeks) basis. At the end of the 3-month treatment exposure period, subjects have ~~extended~~ follow-up to 12 weeks to assess safety **with an optional extended follow up to 48 weeks**.

Section 5.1 Inclusion Criteria, 4(b)

Rationale: To include an optional 9-month off treatment follow up period. Females of reproductive potential will not be on mandatory contraceptive during the optional observational follow-up period

Original text:

Females of reproductive potential (FRP), must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until the final Follow-up visit in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception

Amended text:

Females of reproductive potential (FRP), must agree to follow (or confirm that they have and are currently following) one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see Appendix 4) from at least 28 days prior to the first dose of study treatment until ~~the final~~ Follow-up visit **Day 169** in conjunction with partner's use of male condom. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception

Section 5.1 Inclusion Criteria, 4(d)

Rationale: To include an optional 9-month off treatment follow up period. Males will not be on mandatory contraceptive during the optional observational follow-up period

Original text:

Male subjects with a female partner of child-bearing potential must agree to meet one of the contraception requirements from the time of first dose of study treatment until the final Follow-up visit.

Amended text:

Male subjects with a female partner of child-bearing potential must agree to meet one of the contraception requirements from the time of first dose of study treatment until ~~the final~~ Follow-up visit **day 169**.

Section 5.1 Inclusion Criteria, 4(e)

Rationale: To include an optional 9-month off treatment follow up period. Males will not be on mandatory contraceptive or be asked not to donate sperm during the optional observational follow-up period

Original text:

Male subjects must refrain from donating sperm from the time of first dose of study treatment until the final Follow-up visit.

Amended text:

Male subjects must refrain from donating sperm from the time of first dose of study treatment until ~~the final~~ Follow-up visit **day 169**.

Section 5.1 Inclusion Criteria, 6(b)

Rationale: To provide clarity regarding the inclusion criteria in regards to prior treatment with interferon

Original text:

Part 2: Subjects with CHB receiving stable nucleos(t)ide analogue therapy, defined as no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study.

Amended text:

Part 2: Subjects with CHB receiving stable nucleos(t)ide analogue therapy, defined as no changes to their nucleos(t)ide regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study. **Subjects with prior treatment with interferon (pegylated or non-pegylated) must have ended treatment at least 6 months prior to the Baseline visit (Day 1 pre-dose).**

Section 5.4.4 Renal Function Stopping Criteria, Paragraph 2

Rationale: To provide edits for clarity. Stopping criteria is based on serum creatinine, creatine kinase is a different laboratory marker

Original text:

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 creatinine kinase, serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP), and/or complement panel (C3, C4, C5a and Bb). Further evaluation and actions should be determined by the investigator in consultation with the medical monitor.

Amended text:

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 creatinine ~~kinase~~, serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP), and/or complement panel (C3, C4, C5a and Bb). Further evaluation and actions should be determined by the investigator in consultation with the medical monitor.

Section 5.4.5 Pharmacokinetic Stopping Criteria

Rationale: To provide updates of the pre-clinical data

Original text:

Part 1: Doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma $AUC_{(0-\infty)}$ and C_{max} observed at the NOAEL dose of 30 mg/kg/day in the 13-week monkey toxicity study ($AUC_{(0-\infty)}$ = 465.75 mg•h/mL and C_{max} = 57.9 mg/mL).

A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 465.75 mg•h/mL and 57.9 mg /mL (mean exposures at NOAEL dose in monkey), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection. Dose escalation may be stopped or a smaller dose increment selected (Section 6.3) for the next cohort if the predictive probability of exceeding the mean NOAEL exposure is greater than 50%.

Amended text:

Part 1: Doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma $AUC_{(0-\infty)}$ and C_{max} observed at the NOAEL

dose of 30 mg/kg/day in the 13-week monkey toxicity study ($AUC_{(0-\infty)}$ = ~~465.75~~ **492.7** mg•h/mL and C_{max} = ~~57.9~~ **52.7** mg/mL).

A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than~~465.75~~ **492.7** mg•h/mL and ~~57.9~~ **52.7** mg /mL (mean exposures at NOAEL in the **13-week** monkey **study**), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection. Dose escalation may be stopped or a smaller dose increment selected (Section 6.3) for the next cohort if the predictive probability of exceeding the mean NOAEL exposure is greater than 50%.

Section 5.5 Subject and Study Completion, bullet point 3

Rationale: To update text to include an optional 9-month off treatment follow up period

Original text:

None

Amended text:

- **For subjects who participate in the optional extended post treatment follow-up period, a completed subject in extended follow-up period is one who has completed the Day 450 visit. An ongoing subject who misses the Day 450 visit will be considered as lost to follow up for the optional extended follow-up period.**

Section 6.1 Investigational Product and Other study Treatment, table 6

Rationale: to update the treatments to be studied in Part 2. Since a monthly dose will not be included, the text has been removed

Original text:

Study Treatment		
Product Name:	GSK3389404	Placebo
Formulation Description:	Clear colorless to slightly yellow solution	Clear colorless solution
Dosage Form:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	100 mg/mL; 1.0 mL nominal volume per vial (0.25 mL overfill per vial)	Placebo

Study Treatment		
Product Name:	GSK3389404	Placebo
Route/Administration/Duration:	SC, single and multiple (once weekly, bi-weekly, or once monthly, up to 85 days)	SC, single and multiple (once weekly, bi-weekly, or once monthly, up to 85 days)
Dosing Instructions:	Administer SC	Administer SC
Manufacturer/Source of Procurement:	GSK Global Manufacturing and Supply, Parma (Italy)	Locally sourced normal saline
Method for Individualizing Dosage:	Dispensing into syringes in pharmacy	Dispensing into syringes in pharmacy

GSK = GlaxoSmithKline, SC = subcutaneous

Amended text:

Study Treatment		
Product Name:	GSK3389404	Placebo
Formulation Description:	Clear colorless to slightly yellow solution	Clear colorless solution
Dosage Form:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	100 mg/mL; 1.0 mL nominal volume per vial (0.25 mL overfill per vial)	Placebo
Route/Administration/Duration:	SC, single and multiple (once weekly, bi-weekly~~, or once monthly,~~ up to 85 days)	SC, single and multiple (once weekly, bi-weekly~~, or once monthly,~~ up to 85 days)
Dosing Instructions:	Administer SC	Administer SC
Manufacturer/Source of Procurement:	GSK Global Manufacturing and Supply, Parma (Italy)	Locally sourced normal saline
Method for Individualizing Dosage:	Dispensing into syringes in pharmacy	Dispensing into syringes in pharmacy

GSK = GlaxoSmithKline, SC = subcutaneous

Section 6.1 Investigational Product and Other study Treatment, table 7

Rationale: To update treatments to be studied in Part 2, since 240 mg GSK3389404 as a single injection will not be used, it has been removed from the table

Original text:

Dose[1]	**Volume to Administer**[2]
30 mg or placebo	0.30 mL
60 mg or placebo	0.60 mL
120 mg or placebo	1.2 mL
240 mg or placebo	2.4 mL

3. Dose may change based on safety and pharmacokinetic data from preceding cohort(s)
4. If a change in dose is warranted, volume to administer (mL) = dose (mg)/100

Amended text:

Dose[1]	**Volume to Administer**[2]
30 mg or placebo	0.30 mL
60 mg or placebo	0.60 mL
120 mg or placebo	1.2 mL
~~240 mg or placebo~~	~~2.4 mL~~

1. Dose may change based on safety and pharmacokinetic data from preceding cohort(s)
2. If a change in dose is warranted, volume to administer (mL) = dose (mg)/100

Section 6.2 Treatment Assignment, paragraph 3

Rationale: To update the treatments to be studied in Part 2. To provide clarity on processes

Original text:

Two randomization schedules for Part 2 will be generated after Part 1 is completed and dose levels and regimens for Part 2 have been identified. A separate randomization schedule will be generated for the sentinel group. The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo. Two or 3 dose levels each at 2 different dosing regimens will be explored.

Amended text:

Two randomization schedules for Part 2 will be generated after **dosing in** Part 1 is completed and dose levels and regimens for Part 2 have been identified. A separate randomization schedule will be generated for the sentinel group. The remainder of Part 2 subjects will be centrally randomized using a randomization schedule to receive 1 of the active dose levels and regimens selected in Part 2 or corresponding matching placebo. ~~Two or 3 dose levels each at 2 different dosing regimens will be explored.~~

Section 6.2 Treatment Assignment, randomization table

Rationale: To update the treatments to be studied in Part 2

Original text:

	Sentinel		Remainder	
Part 2	**Active**	**Placebo**	**Active**	**Placebo**
Dose Level 1, Regimen 1[a]	1	1	10	1
Dose Level 1, Regimen 2[a]	1	1	10	1
Dose Level 2, Regimen 1[a]	1	1	10	1
Dose Level 2, Regimen 2[a]	1	1	10	1
Dose Level 3, Regimen 1[a]	1	1	10	1
Dose Level 3, Regimen 2[a]	1	1	10	1

a. The actual dose levels and regimens will be identified after review of data from Part 1. Up to 3 dose levels and 2 regimens will be studied.

Amended text:

	Sentinel		Remainder	
Part 2	**Active**	**Placebo**	**Active**	**Placebo**
60 mg GSK3389404 weekly ~~Dose Level 1, Regimen 1[a]~~	1	1	10	1
120 mg GSK3389404 bi-weekly ~~Dose Level 1, Regimen 2[a]~~	1	1	10	1
120 mg GSK3389404 weekly ~~Dose Level 2, Regimen 1[a]~~	1	1	10	1
~~Dose Level 2, Regimen 2[a]~~	~~1~~	~~1~~	~~10~~	~~1~~
~~Dose Level 3, Regimen 1[a]~~	~~1~~	~~1~~	~~10~~	~~1~~
~~Dose Level 3, Regimen 2[a]~~	~~1~~	~~1~~	~~10~~	~~1~~

~~a. The actual dose levels and regimens will be identified after review of data from Part 1. Up to 3 dose levels and 2 regimens will be studied.~~

Section 6.3 Planned Dose Adjustments, bullet point 1, sub-bullet point 2

Rationale: To provide updates of the pre-clinical data

Original text:

- A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than 465.75 mg•h/mL and 57.9 mg /mL (mean exposures at NOAEL dose in monkey), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection

Amended text:

- A Bayesian predictive probability of $AUC_{(0-\infty)}$ and C_{max} less than~~465.75~~ **492.7** mg•h/mL and ~~57.9~~ **52.7** mg /mL (mean exposures at NOAEL in the **13-**

week monkey **study**), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection

Section 6.5 Blinding, Bullet points 4 and 5

Rationale: To include management review of unblinded data

Original text:

none

Amended text:

- **Management review of unblinded efficacy data is planned for both parts of the study. For part 1, the review provides early information on potential efficacious dose and dose frequency including the need for dose escalation. For part 2, the review will facilitate internal governance decision making on project progress and trigger further studies. Unblinded efficacy data may be provided to the following management/function as required: Senior VP of Infectious Disease Therapy Area, Head Unit Physician, Project Statistician, Head of ID Statistics/Programming, Director of Clinical Pharmacology, Safety Evaluation and Risk Management, Global Regulatory Lead, Project Physician Lead, Clinical Investigator Lead, Clinical Development Manager,Global Marketing Director**
- **The frequency of management review in Part 2 will be synchronized with monthly blinded SRT review of the study. The management review of the Part 1 data will occur as required for decision making.**

Section 6.11.3 Activity

Rationale: To update text to include an optional 9-month off treatment follow up period

Original text:

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. For the duration of the study, until final follow-up, subjects are encouraged to refrain from changing their activity beyond that which they normally perform. While domiciled in the study site, subjects may participate in light recreational activities.

Amended text:

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. For the duration of the study, until final follow-up **(this includes the optional additional follow-up period)**, subjects are encouraged to refrain from changing their activity beyond that which they normally perform. While domiciled in the study site, subjects may participate in light recreational activities.

Section 6.12 Concomitant Medications and Non-Drug Therapies

Rationale: To update text to include an optional 9-month off treatment follow up period

Original text:

All medications taken at any time from 3 months prior to Baseline (Day 1 pre-dose) to the final Follow-up visit will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

Amended text:

All medications taken at any time from 3 months prior to Baseline (Day 1 pre-dose) to the final Follow-up visit **(this includes the optional additional follow-up period)** will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

Section 6.12.2 Prohibited Medications and Non-Drug Therapies

Rationale: To provide clarity regarding the inclusion criteria in regards to prior treatment with interferon

Original text:

none

Amended text:

- **PEG-interferon or other immunomodulating therapies**

Section 7.1 Time and Events Tables, bullet points 1-3

Rationale: To update the time and events tables to reflect treatments to be studied in Part 2 and to include an optional 9-month off treatment follow up period

Original text:

- Once weekly dosing regimen assessments are detailed for the treatment period in Table 11 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 12 (Day 92 to Day 169/ET).

- Bi-weekly dosing regimen assessments are detailed for the treatment period in Table 13 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 14 (Day 92 to Day 169/ET).
- Once monthly dosing regimen assessments are detailed for the treatment period in Table 15 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 16 (Day 92 to Day 169/ET).

Amended text:

- Once weekly dosing regimen assessments are detailed for the treatment period in Table 11 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 12 (Day 92 to Day 169/ET)**, with an optional additional follow-up on Days 270, 360, and 450).**
- Bi-weekly dosing regimen assessments are detailed for the treatment period in Table 13 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 14 (Day 92 to Day 169/ET)**, with an optional additional follow-up on Days 270, 360, and 450)**.
- ~~Once monthly dosing regimen assessments are detailed for the treatment period in Table 15 (Day 1 to Day 85) and for the post-treatment follow-up period in Table 16 (Day 92 to Day 169/ET).~~

Section 7.1 Time and Events Tables, Table 8

Rationale: To clarify that informed consent may be obtained any time prior to screening and is not limited to the 30 day screening window. Please note- only the row/column where changes were made will be shown, not the whole table

Original text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**
Informed Consent	X

Amended text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**
Informed Consent **(obtained any time prior to screening)**	X

Section 7.1 Time and Events Tables, Table 12 Time and Events Table: Day 92 to Day 169 of multiple dose (part 2) once weekly dosing and Table 14 Time and Events Table: Day 92 to Day 169 of multiple dose (part 2) bi-weekly dosing

Rationale: to clarify that pregnancy test should be performed on females of reproductive potential

Original text:

Footnote 6. Female subjects: serum hCG or urine pregnancy test.

Amended text:

Footnote 6. Female subjects **of reproductive potential**: serum hCG or urine pregnancy test.

Section 7.1 Time and Events Tables, Table 15 Time and Events Table: Optional Follow-up Period Day 270 to Day 450 for once weekly and bi-weekly dosing

Rationale: To update the time and events tables to include an optional 9-month off treatment follow up period and the assessments that will occur during the off-treatment follow up period

Original text:

none

Amended text:

Assessment	**Day 270** (±7 days)	**Day 360** (±7 days)	**Day 450** (±7 days)	**ET**
Outpatient visit	**X**	**X**	**X**	**X**
Safety Assessments				
AE/SAE review[1]	← **Continuous** →			**X**
Concomitant medication review	← **Continuous** →			**X**
Brief physical exam	**X**	**X**	**X**	**X**
Vital signs[2]	**X**	**X**	**X**	**X**
Laboratory Assessments[4]				
Pregnancy test (as appropriate)[5]			**X**	**X**
Hematology/Chemistry/Urinalysis[6]	**X**	**X**	**X**	**X**
Urine ACR[5,6]	**X**	**X**	**X**	**X**
Complement (C3/C4)	**X**	**X**	**X**	**X**
PT, INR, aPTT	**X**	**X**	**X**	**X**
hs-CRP	**X**	**X**	**X**	**X**
Archived serum and plasma samples[7]	**X**	**X**	**X**	**X**
HBsAg and HBV DNA	**X**	**X**	**X**	**X**
HBeAg[8]	**X**	**X**	**X**	**X**

Assessment	Day 270 (±7 days)	Day 360 (±7 days)	Day 450 (±7 days)	ET
HBV genotype/phenotype[9]	X	X	X	X
HBsAb	X	X	X	X
Meal[10]	X	X	X	X

ACR = albumin to creatinine ratio, AE/SAE = adverse event/serious adverse event, aPTT = activated partial thromboplastin time, CHB = chronic hepatitis B, ECG = electrocardiogram, ET = early termination, HBeAg = hepatitis B virus e-antigen, HBsAb = hepatitis B virus surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, hCG = human chorionic gonadotropin, hs-CRP = high sensitivity C-reactive protein, INR = international normalized ratio, PK = pharmacokinetics, PT = prothrombin time

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
3. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments.
4. Female subjects of reproductive potential: serum hCG or urine pregnancy test.
5. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessment.
6. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
7. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
8. HBeAg-positive subjects only.
9. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
10. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Section 7.1 Time and Events Tables, old Table 15 and 16

Rationale: To update the time and events tables to reflect treatments to be studied in Part 2. Please note- only the table number and title will be shown in the original text as these tables were deleted since once monthly dosing will not be studied in Part 2

Original text:

Table 15 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Monthly Dosing

Table 16 Time and Events Table: Day 92 to Day 169 of Multiple Dose (Part 2) Once Monthly Dosing

Amended text:

~~Table 15 Time and Events Table: Day 1 to Day 85 of Multiple Dose (Part 2) Once Monthly Dosing~~

~~Table 16 Time and Events Table: Day 92 to Day 169 of Multiple Dose (Part 2) Once Monthly Dosing~~

Section 7.2 Screening and Critical Baseline Assessments, last sentence

Rationale: To update the text and Table numbers to reflect treatments to be studied in Part 2

Original text:

Baseline assessments are provided in Table 9 for Part 1, and Table 11, Table 13, and Table 15 for Part 2.

Amended text:

Baseline assessments are provided in Table 9 for Part 1, and Table 11~~,~~ **and** Table 13~~, and Table 15~~ for Part 2.

Section 7.3.2 Pregnancy

Rationale: To provide clarity regarding contraceptive use in male subjects with female partners who are currently pregnant

Original text:

none

Amended text:

- **Male subjects with female partners who are currently pregnant should comply with the acceptable contraceptive requirement as detailed in the protocol. No precautions are required for the male subject's pregnant partner.**

Section 7.3.5 Vital Signs, bullet point 2

Rationale: To provide clarity on order of assessments by investigator request

Original text:

During visits where a 12-lead ECG and/or blood collection is also required, vital sign measurements will be taken after the ECG and prior to scheduled blood collection (which should be drawn at the exact nominal time point).

Amended text:

~~During visits where a 12-lead ECG and/or blood collection is also required, vital sign measurements will be taken after the ECG and prior to scheduled blood collection (which should be drawn at the exact nominal time point).~~

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

Section 7.3.6 Electrocardiogram, bullet point 2

Rationale: To provide clarity on order of assessments by investigator request

Original text:

During visits where vital signs and/or blood collection is also required, vital sign measurements will be taken after the ECG and prior to scheduled blood collection (which should be drawn at the exact nominal time point).

Amended text:

~~During visits where vital signs and/or blood collection is also required, vital sign measurements will be taken after the ECG and prior to scheduled blood collection (which should be drawn at the exact nominal time point).~~

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

Section 9.1 Hypotheses, last sentence

Rationale: To provide updates in the statistical section based on the change in total subject number

Original text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 95%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥95%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Amended text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 9**0**~~5~~%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥9**0**~~5~~%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Section 9.2.1 Sample Size Assumptions, second paragraph

Rationale: To provide updates from Part 1, to update the treatment and populations to be studied in Part 2, and to update statistical text to support selection of treatment and populations to be studied in Part 2

Original text:

In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. The exact number of subjects to be enrolled will be data driven from Part 1 and will depend on the number of dose levels selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate 14% overall drop-out rate, so that there are approximately 10 evaluable subjects in each of the active treatment group and approximately 12 subjects in the placebo group. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and dosing regimen. The total sample size will provide sufficient power to select an efficacious treatment group using a Bayesian model based approach sharing common degrees of freedom across treatment arms. Assuming 3 dose levels and 2 dosing regimens are selected in Part 2, the probability of declaring success of an inefficacious treatment arm (with RR ≤5%) is less than 14%. On the other hand if an active treatment arm has a 30% RR, the probability of selecting the treatment arm is about 80% under the model assumption. Appendix 6 (Section 12.6) details the operating characteristics of the design.

Amended text:

In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. ~~The exact number of subjects to be enrolled will be data driven from Part 1 and will depend on the number of dose levels selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate 14% overall drop-out rate, so that~~ **T**~~t~~here are approximately 1**1**~~0~~ evaluable subjects in each of the active treatment group and approximately ~~12~~ **6** subjects in the placebo group. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the

similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and dosing regimen. The total sample size will provide sufficient power to select an efficacious treatment group using a Bayesian model based approach sharing common degrees of freedom across treatment arms. ~~Assuming 3 dose levels and 2 dosing regimens are selected in Part 2~~**With the 3 treatment groups selected for Part 2**, the probability of declaring success of an inefficacious treatment arm (with RR ≤5%) is less than 14%. On the other hand if an active treatment arm has a 30% RR, the probability of selecting the treatment arm is about 80% under the model assumption. Appendix 6 (Section 12.6) details the operating characteristics of the design.

Section 9.2.2 Sample Size Sensitivity, first sentence

Rationale: To update statistical text to provide the sample size and treatments selected for Part 2

Original text:

Sample size sensitivity of Part 2 will be provided after dose levels and regimens are selected from Part 1.

Amended text:

~~Sample size sensitivity of Part 2 will be provided after dose levels and regimens are selected from Part 1.~~

Section 9.3.3 Interim Analysis and Final Analysis, second paragraph

Rationale: To provide updates of the pre-clinical data

Original text:

During Dose escalation, a Bayesian predictive probability of mean $AUC_{(0-\infty)}$ and C_{max} less than 465.75 mg•h/mL and 57.9 mg /mL (mean exposures at NOAEL dose in monkey), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection.

Amended text:

During Dose escalation, a Bayesian predictive probability of mean $AUC_{(0-\infty)}$ and C_{max} less than ~~465.75~~ **492.7** mg•h/mL and ~~57.9~~ **52.7** mg /mL (mean exposures at NOAEL in the **13-week** monkey **study**), respectively, will be calculated for the next dose level and used together with safety and tolerability data to aid next dose selection.

Section 9.3.3.3 Part 2: 3 month follow up analysis

Rationale: To include analysis at original end of study timepoint (Day 169), as an optional additional follow-up period is added to Part 2

Original text:

none

Amended text:

The 3 month follow up analysis for Part 2 will be conducted once last randomized subject has completed the Day 169 visit.

Section 9.3.3.4 Part 2: 6 month follow up analysis

Rationale: To include analysis at the mid-point (6 month timepoint) of the total follow-up period of Part 2 (total follow-up period is approx. 12 months from last dose to final follow-up visit of the optional additional follow up period)

Original text:

none

Amended text:

The 6 month follow up analysis for Part 2 may be conducted once last randomized subject has completed the Day 270 visit to support internal decision making and/or regulatory interaction.

Section 9.3.3.5 Part 2: End of Study Analysis

Rationale: To update definition of the end of study analysis to include data collected through the optional additional follow up period

Original text:

The end of study analysis for Part 2 will be conducted once the last randomized subject (sentinel, remainder of subjects, and the optional Japanese Part 2 sub-study subjects if applicable) has completed the Day 169 visit.

Amended text:

The end of study analysis for Part 2 will be conducted once the last subject **participating in the optional follow-up** ~~randomized subject (sentinel, remainder of subjects, and the optional Japanese Part 2 sub-study subjects if applicable)~~ has completed the Day **450** ~~169~~ visit.

Section 9.4.1 Primary Analyses, Efficacy, 11th paragraph

Rationale: To update the statistical section based on the change in total subject number

Original text:

In Part 2, GSK3389404 treatment efficacy will be declared if the posterior probability that the difference in the RRs between that active group and the placebo is positive and is high (at least 95%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥95%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Amended text:

An active treatment group In Part 2, GSK3389404 treatment efficacy will be declared if the posterior probability that the difference in the RRs between that active group and the placebo is positive and is high (at least 9**0**~~5~~%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥9**0**~~5~~%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Section 10.8.1 Dose Escalation Committee, 2nd paragraph

Rationale: To provide updates of the pre-clinical data

Original text:

A maximum $AUC_{(0-\infty)}$ of 465.75 μg•h/mL or C_{max} of 57.9 μg/mL of GSK3389404 is not expected to be exceeded in any cohort.

Amended text:

A maximum $AUC_{(0-\infty)}$ of ~~465.75~~ **492.7** mg•h/mL or C_{max} of ~~57.9~~ **52.7** mg /mL of GSK3389404 is not expected to be exceeded in any cohort.

Section 11. References

Rationale: To update reference

Original text:

GlaxoSmithKline Document Number 2015N236049_02. Investigator's Brochure (IB) for GSK3389404. 2017.

Amended text:

GlaxoSmithKline Document Number 2015N236049_0~~2~~**4**. Investigator's Brochure (IB) for GSK3389404. 201~~6~~**8**.

Section 12.6.1 Introduction, paragraph 3 and 4.

Rationale: To update the number of subjects based on number of subjects enrolled for Part 1 and expected number of subjects in Part 2 based on estimated number of subjects after selecting treatment arms for Part 2

Original text:

In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. The exact number of subjects to be enrolled will be data driven from Part 1 and will depend on the number of dose levels selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate 14% overall drop-out rate, so that there are approximately 10 evaluable subjects in each of the active treatment group and approximately 12 subjects in placebo. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and regimen.

The dosing regimens for selected treatment groups will be identical. For example, if 480 mg is selected for Part 2, other selected treatment groups will also be administered in a weekly and bi-weekly (every 2 weeks) dosing regimen.

Amended text:

In Part 2, approximately 80 subjects with CHB are planned for randomization to study treatment. ~~The exact number of subjects to be enrolled will be data driven from Part 1 and will depend on the number of dose levels selected for Part 2. For example, if 3 dose levels each with 2 dosing regimens are selected in Part 2, approximately 80 subjects will be randomized in the 7 treatment groups (6 active groups and 1 placebo group). Enrolling approximately 80 subjects will allow for an approximate 14% overall drop-out rate, so that~~ **T**~~t~~here are approximately 1**1**~~0~~ evaluable subjects in each of the active treatment group and approximately ~~12~~ **6** subjects in placebo. Matching placebo injections will be prepared for each dose level and dosing regimen and will be administered in the similar way of the corresponding active treatment group. Approximately 2 subjects will be randomized in each placebo dose level and regimen.

~~The dosing regimens for selected treatment groups will be identical. For example, if 480 mg is selected for Part 2, other selected treatment groups will also be administered in a weekly and bi-weekly (every 2 weeks) dosing regimen.~~

Section 12.6.3 Success Criteria paragraph 1

Rationale: to update statistical sections

Original text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 95%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥95%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Amended text:

An active treatment group will be declared efficacious if the posterior probability that the difference in the RRs between that active group and the placebo is positive, is high (at least 9~~5~~**0**%), i.e., P ($RR_{ACT} > RR_{PBO}$) ≥9~~5~~**0**%, where RR_{ACT} is the RR in the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

Section 12.6.4 Scenarios for Testing

Rationale: To update the text with treatments selected for Part 2

Original text:

It is assumed that 3 dose levels (120, 240, and 480 mg) each at 2 regimens (weekly and biweekly) will be selected in Part 2. The description of treatment groups along with the sample size is provided in Table 18 A wide range of scenarios, as described in Table 19, were created to test the model performance.

Amended text:

The dose levels and regimens selected for Part 2 are 60 mg GSK3389404 weekly, 120 mg bi-weekly GSK3389404, 120 mg GSK3389404 weekly or placebo. ~~It is assumed that 3 dose levels (120, 240, and 480 mg) each at 2 regimens (weekly and bi-weekly) will be selected in Part 2.~~ The description of treatment groups along with the sample size is provided in Table ~~18~~ **17** A ~~wide~~ range of scenarios, as described in Table ~~19~~ **18**, were created to test the model performance.

Section 12.6.4 Scenarios for Testing, previously Table 18 and 19

Rationale: To update with treatments selected for Part 2

Original text:

Table 18 Treatment Description

Treatment Description	Treatment	Sample Size
Total monthly dose of 120 mg divided weekly (i.e., 30 mg once a week)	120W	10
Total monthly dose of 120 mg divided bi-weekly (i.e., 60 mg bi-weekly)	120BW	10
Total monthly dose of 240 mg divided weekly (i.e., 60 mg once a week)	240W	10
Total monthly dose of 240 mg divided bi-weekly (i.e., 120 mg bi-weekly)	240BW	10
Total monthly dose of 480 mg divided weekly (i.e., 120 mg once a week)	480W	10
Total monthly dose of 480 mg divided bi-weekly (i.e., 240 mg bi-weekly)	480BW	10
Matching placebo for each active treatment	PBO	12

Table 19 Scenarios for Simulation

Scenario Number	Response Rate (%) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW)	Description
1	(5, 5, 5, 5, 5, 5, 5)	No treatment effect
2	(5, 20, 20, 20, 20, 20, 20)	All of the active treatment groups are equally effective (low effect size)
3	(5, 30, 30, 30, 30, 30, 30)	All of the active treatment groups are equally effective (medium effect size)
4	(5, 10, 15, 20, 25, 30, 35)	Larger effect in higher dose group, bi-weekly dosing regimen is more efficacious than weekly
5	(5, 15, 10, 25, 20, 35, 30)	Larger effect in higher dose group, weekly dosing regimen is more efficacious than bi-weekly y
6	(5, 10, 10, 10, 10, 10, 30)	Only 480 mg (highest dose) bi-weekly dosing is efficacious
7	(5, 10, 10, 10, 10, 20, 30)	Only 480 mg (highest dose) has dose response, bi-weekly having medium and weekly having small effect
8	(5, 10, 10, 10, 30, 10, 10)	Only 240 mg (middle dose) bi-weekly dosing is efficacious
9	(5, 10, 30, 10, 10, 10, 10)	Only 120 mg (lowest dose) bi-weekly dosing is efficacious

Amended text:

Table 178 Treatment Description

Treatment Description	Treatment	Sample Size
~~Total monthly dose of 120 mg divided weekly (i.e., 30 mg once a week)~~	~~120W~~	~~10~~
~~Total monthly dose of 120 mg divided bi-weekly (i.e., 60 mg bi-weekly)~~	~~120BW~~	~~10~~
Total monthly dose of 240 mg divided weekly (i.e., 60 mg once a week)	240W	1~~0~~**1**
Total monthly dose of 240 mg divided bi-weekly (i.e., 120 mg bi-weekly)	240BW	1~~0~~**1**
Total monthly dose of 480 mg divided weekly (i.e., 120 mg once a week)	480W	1~~0~~**1**
~~Total monthly dose of 480 mg divided bi-weekly (i.e., 240 mg bi-weekly)~~	~~480BW~~	~~10~~
Matching placebo for each active treatment	PBO	~~12~~ **6**

Table 189 Scenarios for Simulation

Scenario Number	Response Rate (%) (PBO, ~~120W, 120BW,~~ 240W, 240BW, 480W~~, 480BW~~)	Description
1	(5, 5, 5, 5, ~~5, 5, 5~~)	No treatment effect
~~2~~	~~(5, 20, 20, 20, 20, 20, 20)~~	~~All of the active treatment groups are equally effective (low effect size)~~
~~3~~**2**	(5, 30, 30, 30~~, 30, 30, 30~~)	All of the active treatment groups are equally effective (medium effect size)
~~4~~ **3**	(5, **15, 15, 35,** ~~10, 15, 20, 25, 30, 35~~)	Larger effect in higher dose group, bi-weekly dosing regimen is **equally effective as**~~more efficacious than~~ weekly
~~5~~ **4**	(5, **20, 15, 35,** ~~15, 10, 25, 20, 35, 30~~)	Larger effect in higher dose group, weekly dosing **has small effect** ~~regimen is more efficacious than bi-weekly~~ **y**
~~6~~	~~(5, 10, 10, 10, 10, 10, 30)~~	~~Only 480 mg (highest dose) bi-weekly dosing is efficacious~~
~~7~~	~~(5, 10, 10, 10, 10, 20, 30~~)	~~Only 480 mg (highest dose) has dose response, bi-weekly having medium and weekly having small effect~~
~~8~~	~~(5, 10, 10, 10, 30, 10, 10)~~	~~Only 240 mg (middle dose) bi-weekly dosing is efficacious~~
~~9~~	~~(5, 10, 30, 10, 10, 10, 10)~~	~~Only 120 mg (lowest dose) bi-weekly dosing is efficacious~~

Section 12.6.5 Simulations, paragraph 1, 2nd sentence

Rationale: To update with treatments selected for Part 2

Original text:

Response data for 7 treatment groups are generated from binomial distributions using the sample size from Table 18 and response rates from Table 19.

Amended text:

Response data for ~~7~~ **3** treatment groups are generated from binomial distributions using the sample size from Table **17**~~18~~ and response rates from Table **18**~~19~~.

Section 12.6.5 Simulations, paragraph 1, 4th sentence

Rationale: To update with treatments selected for Part 2

Original text:

For each of the scenarios, average posterior means along with 90% credible intervals (CI), average PoS, and probability of selecting a dose group based on PoS are calculated over the sample space of 1000 simulations.

Amended text:

For each of the scenarios, average posterior means along with 90% credible intervals (CI), **and** average PoS~~, and probability of selecting a dose group based on PoS~~ are calculated over the sample space of 1000 simulations.

Section 12.6.5 Simulations, 2nd paragraph, last sentence

Rationale: To update with treatments selected for Part 2

Original text:

The BLRM was not able to select the efficacious treatment group under Scenario 7, 8 and 9, where there is no monotonic relationship between dose and response. These scenarios are unlikely to happen in real life.

Amended text:

~~The BLRM was not able to select the efficacious treatment group under Scenario 7, 8 and 9, where there is no monotonic relationship between dose and response. These scenarios are unlikely to happen in real life.~~

Section 12.6.5 Simulations, paragraph 3 and 4

Rationale: To update statistical section

Original text:

A cutoff point of 90% for PoS seems to provide reasonable probability for selecting an efficacious dose group given the sample size of this study

Amended text:

A cutoff point of ~~95~~ **90**% for PoS seems to provide reasonable probability for selecting an efficacious dose group given the sample size of this study

Section 12.6.5 Simulations, Table 19, 20, 21, 22

Rationale: To update with treatments selected for Part 2

Original text:

none

Amended text:

Table 19 Simulation Results from Scenario 1

	Scenario 1		No Treatment Effect						
			(PBO, 240W, 240BW, 480W): (5, 5, 5, 5)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]		Power[2] Cutoff Points			
						85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.71)						
	240W	6.05	(0.81,16.59)	53.17		30.8	30.8	8.2	1.6
	240BM	5.72	(0.67,16.09)	53.05		31.4	31.4	6.2	0.8
	480W	5.46	(0.63,15.53)	51.86		28.7	28.7	6.6	0.6
BLRM	PBO	6.95	(0.71,21.34)						
	240W	4.88	(0.56,14.02)	57.83		21.9	11.0	3.1	0.3
	240BW	5.3	(0.55,15.34)	58.67		31.4	13.8	3.9	0.3
	480W	5.13	(0.52,15.04)	57.84		28.7	13.7	4.7	0.2

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, , a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected
2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Table 20 Simulation Results from Scenario 2

	Scenario 2		All of the active treatment groups are equally effective (medium effect size)						
			(PBO, 240W, 240BW, 480W): (5, 30, 30, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]		Power[2] Cutoff Points			
						85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)						
	240W	30.93	(12.67,53.01)	88.77		75.8	75.7	66.0	49.1
	240BM	30.09	(12.01,52.13)	88.26		75.9	75.8	65.7	49.1
	480W	30	(11.85,52.15)	88.6		75.8	75.8	66.2	49.2
BLRM	PBO	6.95	(0.71,21.34)						
	240W	30.38	(12.62,51.95)	89.53		76.2	74.1	64.9	46.7
	240BW	29.88	(12.05,51.71)	88.8		75.9	75.4	65.2	47.7
	480W	29.77	(11.84,51.77)	89.02		75.8	75.0	65.9	48.9

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, , a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected
2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Table 21 Simulation Results from Scenario 3

	Scenario 3		Larger effect in higher dose group, bi-weekly dosing is equally effective as weekly						
			(PBO, 240W, 240BW, 480W): (5, 15, 15, 35)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]		Power[2] Cutoff Points			
						85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)						
	240W	16.23	(4.27,34.07)	74.83		61.0	61.0	36.9	17.7
	240BM	15.58	(3.89,33.22)	74.26		60.3	60.2	37.7	15.5
	480W	34.86	(15.25,57.59)	91.23		80.5	80.4	70.9	58.3
BLRM	PBO	6.95	(0.71,21.34)						
	240W	16.27	(4.42,34.06)	79		61.0	56.7	35.2	15.1
	240BW	15.28	(3.81,32.93)	77.24		60.3	55.0	36.8	12.1
	480W	33.72	(14.57,56.2)	90.88		80.5	77.6	69.2	54.0

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, , a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected
2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Table 22 Simulation Results from Scenario 4

	Scenario 4		Larger effect in higher dose group, weekly dosing small effect (PBO, 240W, 240BW, 480W): (5, 20, 15, 35)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]		Power[2] Cutoff Points			
						85%	90%	95%	98%
Pairwise	PBO	6.82	(0.71,20.7)						
	240W	20.9	(6.61,40.53)	80.33		65.9	65.9	48.5	27.8
	240BM	15.58	(3.89,33.2)	74.25		60.3	60.2	37.7	15.5
	480W	34.86	(15.24,57.6)	91.24		80.5	80.3	71.0	58.2
BLRM	PBO	6.95	(0.71,21.34)						
	240W	20.41	(6.57,39.67)	82.65		65.8	63.1	47.0	22.4
	240BW	15.61	(3.95,33.45)	77.78		60.3	56.7	37.0	12.7
	480W	34	(14.77,56.48)	91.03		80.5	77.8	69.2	55.0

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$, , a dose group will be considered efficacious if the PoS is at least 90%, treatment group with highest PoS will be selected
2. Power is defined as proportion of simulation samples where PoS is greater than various cutoff points(85,90,95,98%) over the sample space (i.e., 1000 simulations)

Section 12.6.5 Simulations, Table 24, 25, 26, 27

Rationale: To update with treatments selected for Part 2.

Original text:

Table 24 Simulation Results From Scenario 5

	Scenario 5		Larger effect in higher dose group (weekly dosing regimen is more efficacious than bi-weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 15, 10, 25, 20, 35, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.89	(0.79,16.01)						
	120W	15.35	(3.59,33.51)	71.91	No	47.6	47.5	39.4	24.8
	120BW	11.1	(2.15,26.26)	62.23	No	37.0	37.0	30.4	14.5
	240W	25.26	(8.64,47)	85.09	No	69.8	68.6	56.4	40.6
	240BW	20.61	(6.01,41.08)	80.06	No	60.1	59.6	48.8	33.6
	480W	34.72	(14.63,58.19)	92.29	No	82.2	81.0	71.5	58.2
	480BW	29.63	(11.11,52.59)	89.04	No	74.8	73.5	62.9	50.5
BL	PBO	5.94	(0.78,16.27)						
	120W	15.25	(5.19,29.7)	80.12	No	59.9	54.1	43.2	26.1

	Scenario 5		Larger effect in higher dose group (weekly dosing regimen is more efficacious than bi-weekly) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 15, 10, 25, 20, 35, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	120BW	12.13	(3.73,24.83)	75.49	No	54.4	48.7	36.6	17.9
	240W	22.52	(11.48,35.84)	90.03	No	77.1	69.2	59.2	47.2
	240BW	18.06	(8.32,30.36)	85.58	No	66.8	60.3	52.1	41.1
	480W	35.7	(18.03,55.74)	95.35	Yes	90.0	85.7	77.4	66.1
	480BW	29.84	(13.75,49.13)	92.59	No	83.6	76.5	66.9	57.2

BLRM = Bayesian logistic regression model; BW = bi-weekly' CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 25 Simulation Results From Scenario 6

	Scenario 6		Only 480 mg (highest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 10, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.87	(0.79,15.98)						
	120W	10.69	(1.94,25.78)	62.31	No	37.2	37.0	30.4	12.7
	120BW	11.31	(2.13,26.85)	63.39	No	38.8	38.7	31.9	16.3
	240W	10.53	(1.97,25.28)	60.78	No	35.5	35.5	29.5	14.6
	240BW	10.35	(1.88,25.04)	60.98	No	35.3	35.3	29.3	13.3
	480W	10.53	(1.94,25.35)	61.14	No	36.8	36.8	31.0	14.1
	480BW	30.59	(11.86,53.5)	89.42	No	77.5	75.8	64.7	50.6
BLRM	PBO	5.92	(0.79,16.22)						
	120W	7.32	(1.61,17.24)	63.74	No	42.8	34.4	19.3	5.6
	120BW	11.45	(2.99,24.92)	72.63	No	51.6	45.2	32.2	15.2
	240W	8.71	(2.78,17.53)	69.47	No	48.7	42.0	29.4	11.5
	240BW	14.46	(5.92,25.8)	80.12	No	57.4	53.1	46.3	29.5
	480W	14.24	(4.08,29.58)	77.18	No	55.6	50.3	40.5	21.9
	480BW	23.65	(9.2,42.41)	86.9	No	73.6	66.4	56.9	43.1

BLRM = Bayesian logistic regression model; CI = credible interval; M = monthly; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 26 Simulation Results From Scenario 7

	Scenario 7		Only 480 mg (highest dose) is efficacious (bi-weekly having medium effect and weekly having small effect) (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 10, 20, 30)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.87	(0.75,16.07)						
	120W	10.72	(1.97,25.75)	61.57	No	36.0	35.9	29.3	14.5
	120BW	11.17	(2.09,26.61)	62.83	No	37.6	37.5	31.2	16.0
	240W	11.63	(2.31,27.22)	63.58	No	39.7	39.7	31.9	15.6
	240BW	10.33	(1.75,25.33)	61.66	No	35.4	35.3	29.2	12.0
	480W	20.8	(6.04,41.54)	80.43	No	59.3	58.8	49.4	35.5
	480BW	30.47	(11.72,53.52)	89.53	No	77.1	76.1	63.1	50.7
BLRM	PBO	5.92	(0.75,16.3)						
	120W	8.21	(1.95,18.74)	65.9	No	45.8	36.6	21.4	7.1
	120BW	9.72	(2.41,21.68)	69.54	No	48.2	41.4	26.6	11.7
	240W	11.71	(4.35,21.99)	75.37	No	55.6	50.8	39.0	20.5
	240BW	14.19	(5.68,25.54)	80	No	57.1	52.0	45.8	29.5
	480W	21.44	(7.88,39.61)	85.58	No	67.5	62.4	54.7	40.1
	480BW	25.9	(10.63,45.2)	89.37	No	76.2	70.4	59.8	46.9

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 27 Simulation Results From Scenario 8

	Scenario 8		Only 240 mg (middle dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 30, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.4	(0.68,15.04)						
	120W	11.04	(2.04,26.4)	64.38	No	41.0	40.9	33.3	15.2
	120BW	9.94	(1.76,24.3)	61.6	No	37.8	37.7	29.2	12.0
	240W	11.05	(2.07,26.33)	64.22	No	41.1	41.1	34.2	16.0
	240BW	31.46	(12.39,54.59)	90.34	No	78.3	77.6	67.1	56.3
	480W	10.44	(1.94,25.16)	62.3	No	38.3	38.3	32.1	14.4

	Scenario 8		Only 240 mg (middle dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 10, 10, 30, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
	480BW	10.67	(1.88,25.83)	63.48	No	39.1	39.0	33.4	15.7
BLRM	PBO	5.46	(0.68,15.33)						
	120W	10.68	(2.74,23.46)	73.45	No	54.8	47.5	31.9	14.2
	120BW	16.98	(5.46,33.5)	82.05	No	65.7	60.4	49.8	32.8
	240W	9.5	(3.19,18.68)	73.12	No	55.6	46.6	34.0	15.6
	240BW	15.38	(6.6,26.82)	82.64	No	64.3	58.6	51.9	36.4
	480W	10.85	(2.82,23.76)	73.32	No	55.2	48.9	32.9	14.7
	480BW	17.12	(5.49,33.79)	82.42	No	65.1	59.7	49.2	33.3

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

1. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
2. A dose group will be selected if the PoS is at least 95%
3. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Table 28 Simulation Results From Scenario 9

	Scenario 9		Only 120 mg (lowest dose) bi-weekly dosing is efficacious (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 30, 10, 10, 10, 10)						
	Treatment	Posterior RR (%)	90% CI	PoS[1]	Decision[2] (Select dose)	Power[3] Cutoff Points			
						85%	90%	95%	98%
Pairwise Comparison	PBO	5.84	(0.79,15.87)						
	120W	10.47	(1.86,25.38)	61.37	No	35.4	35.4	28.2	14.3
	120BW	31.02	(11.9,54.34)	90.87	No	79.1	77.5	66.3	52.1
	240W	10.6	(1.86,25.73)	62.39	No	36.5	36.5	30.5	13.4
	240BW	10.27	(1.82,24.96)	61.21	No	36.5	36.5	30.6	12.8
	480W	11.23	(2.12,26.65)	63.35	No	38.0	38.0	30.6	15.1
	480BW	10.74	(1.97,25.76)	61.98	No	37.5	37.3	30.4	15.1
BLRM	PBO	5.89	(0.79,16.13)						
	120W	14.42	(4.15,29.85)	78.21	No	56.9	51.9	38.4	23.4
	120BW	23.62	(9.06,42.55)	87.68	No	74.0	67.7	57.3	44.0
	240W	8.89	(2.88,17.79)	70.22	No	50.0	41.3	29.1	13.1
	240BW	14.44	(5.85,25.85)	80.92	No	61.0	55.3	45.8	31.4
	480W	7.49	(1.68,17.48)	64.06	No	42.2	33.1	20.1	7.6
	480BW	11.39	(2.93,24.87)	73.07	No	51.7	46.0	33.1	14.8

Scenario 9		**Only 120 mg (lowest dose) bi-weekly dosing is efficacious** (PBO, 120W, 120BW, 240W, 240BW, 480W, 480BW): (5, 10, 30, 10, 10, 10, 10)			
				Decision[2] (Select dose)	**Power[3]**
Treatment	**Posterior RR (%)**	**90% CI**	**PoS[1]**		**Cutoff Points**

BLRM = Bayesian logistic regression model; BW = bi-weekly; CI = credible interval; PBO = placebo; PoS = probability of success; RR = response rate; W = weekly

2. PoS is defined as $P(RR_{ACT} > RR_{PBO})$
3. A dose group will be selected if the PoS is at least 95%
4. Power is defined as percentage of time PoS >95% over the sample space (i.e., 1000 simulations)

Amended text:

Deleted tables

12.7.6. Protocol changes for Amendment 06 (05-JUN-2018) from Protocol Amendment 05 (06-MAR-2018)

Protocol Amendment 6 replaces Protocol Amendment 05 (06-MAR-2018) and applies to all study sites.

Protocol Amendment 06 Summary:

Protocol Amendment 6 is being implemented for the following reasons:

To correct the planned study duration for subjects

- **Rationale:** The planned study duration was incorrect as it did not include the screening window period of 30 days (+15 days exceeding the 30 day screening window where subjects may still be considered eligible after undergoing a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility). As Part 1 is complete, changes to Part 1 figure and wording has not been changed.

To allow inclusion of subjects with ALT $\leq$ 2 X ULN

- **Rationale:** After feedback from investigators, inclusion criterion 9b was changed to allow ALT $\leq$ 2XULN. This change was supported by feedback that factors other than HBV may contribute to slightly elevated ALT levels in subjects.

To add greater clarity for exclusion 4,8g, 9, and 11.

- **Rationale:** After feedback from investigators, exclusion criterion 4 was edited to include exclusion of subjects who the investigator believes may have liver cirrhosis without requiring a positive liver biopsy, Fibroscan, and/or APRI/Fibrosure result to exclude the subject.
- It was noted that sites may use an online calculator that converts the ACR to mg/g instead of mg/mg. The exclusion criterion 8g now includes the ACR cut-off in mg/mg and mg/g. It was also noted that in some cases, subjects have both low urine albumin and low urine creatinine resulting in a high ACR calculation. Wording was added that the investigator should confirm that the patient does not have risk factors that may affect renal function and discuss eligibility with the PPD or GSK medical monitor, or designee since the high ACR may not be clinically relevant in all situations.
- Exclusion criterion 9 indicated that subjects should be excluded based on a mean of triplicate measurements with Fridericia's QT correction formula (QTcF) $\geq$450 msec, however the Time and Events Table 8 for screening indicate that ECG at screening should be single, not triplicate. It has been clarified that if the single ECG at screening shows QTcF $\geq$ 450 msec, a mean of triplicate measurements should be used to confirm that subject meets exclusion criterion.
- Investigators pointed out that some subjects use topical or inhaled corticosteroids, which would not result in the immunosuppressing effects.

Therefore, the exclusion criterion 11 has been clarified to allow for topical/inhaled steroid use.

To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

- **Rationale:** It was not clear how investigators were to determine follow-up visit schedules for subjects who stop treatment (GSK3389404 or placebo), but who are not withdrawn from the study.

To update the Time and Events Table for the optional follow-up period

- Rationale: The primary purpose of the optional follow-up period is to assess long-term efficacy of GSK3389404 and not safety. Therefore, extensive safety assessments were removed from the follow-up period.

To update the unblinded senior management review

- **Rationale:** as internal GSK roles/title names may change, the wording was changed to clarify that senior management may review the data

To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period).

- **Rationale:** Some assessments/requirements were specified to end with the final follow up visit, which in previous versions of the protocol was Day 169. For each case, the final follow-up has been clarified to be Day 169 or Day 450 (if subjects consent to the optional extended follow-up period).

To make edits for clarity

- **Rationale:** Edits were made to the NOAEL- the units for the NOAEL in the 13-week monkey toxicity study were incorrectly written as the NOAEL of 30 mg/kg/day, when it should be mg/kg/week. This does not affect the Cmax/AUC calculations for the NOAEL. Edits were made to better clarify that treatment selections were made for Part 2 based on data from Part 1. Edits were made to make clear that 12 subjects were enrolled for the completed Part 1 of study 205670. Edits were made to remove the word “pharmacy” for dispensing investigational product (IP; GSK3389404 or placebo), as not all sites use a formal pharmacy to dispense IP. Edits were made to make clear that only subjects of reproductive potential should undergo pregnancy testing. Edits were made to ensure that the superscripts/footnote numbers were appropriately matched. Edits were made to clarify that China may also use local laboratory result (urine drug test) for screening as it is not available at the China central laboratory. Edits were made to clarify that there were no requirements to Ip and nucleos(t)ide dosing order. Edits were made to correct the table numbering. Edits were made to correct Table 20, as it was missing a column. Edits were made to correct typos.

List of Changes

Overall Design, 5th paragraph
Rationale: To make edits for clarity- to better clarify that treatment selections were made for Part 2 based on data from Part 1

Original text:
Part 1 (through Day 3). The treatments selected are 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo.

Amended text:
Part 1 (through Day 3). The treatments **that were** selected **for Part 2 based on data from Part 1** are 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo.

Treatment Arms and Duration, Part 1, 1st bullet
Rationale: To correct the planned study duration

Original text:
- A 30-day screening window is planned

Amended text:
- A 30-day screening window is planned
    - **Eligible subjects who fall within a 45-day window (15 days exceeding the 30-day screening window) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility.**

Treatment Arms and Duration, Part 2, 1st sentence
Rationale: To correct the planned study duration

Original text:
In Part 2, 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo are planned and the total study duration, including screening, dosing, and post-treatment follow-up, is not expected to exceed 65 weeks for each subject.

Amended text:
In Part 2, 60 mg GSK3389404 weekly, 120 mg GSK3389404 bi-weekly, 120 mg GSK3389404 weekly or placebo are planned and the total study duration, including screening, dosing, and post-treatment follow-up, is not expected to exceed ~~65~~**71** weeks for each subject.

Treatment Arms and Duration, Part 2, 1st bullet
Rationale: To correct the planned study duration

Original text:

- A 30-day screening window is planned

Amended text:

- A 30-day screening window is planned
    - **Eligible subjects who fall within a 45-day window (15 days exceeding the 30-day screening window) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility.**

Treatment Arms and Duration, Part 2, 3rd bullet
Rationale: To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period)

Original text:

- A post-treatment follow-up period is planned where subjects will present for study visits on Days 85, 92, 99, 113, 141, and 169.

Amended text:

- A **protocol mandated** post-treatment follow-up period is planned where subjects will present for study visits on Days 85, 92, 99, 113, 141, and 169.

Type and Number of Subjects, 1st paragraph, last sentence
Rationale: To provide clarity- to allow for possibility that sites may not be able to recruit HBeAg-positive or negative subjects

Original text:
For Part 2, both HBeAg-positive and HBeAg-negative subjects will be enrolled.

Amended text:
For Part 2, both HBeAg-positive and/**or** HBeAg-negative subjects will be enrolled.

Type and Number of Subjects, 1st bullet point
Rationale: To make edits for clarity- to make clear that 12 subjects were enrolled for the completed Part 1 of study 205670

Original text:

- In Part 1, approximately 20 to 40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol. Twelve subjects were enrolled for part 1 and Part 1 has completed enrollment.

Amended text:

- In Part 1, **twelve subjects were enrolled. Originally** approximately 20 to

40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol. ~~Twelve subjects were enrolled for part 1 and Part 1 has completed enrollment.~~

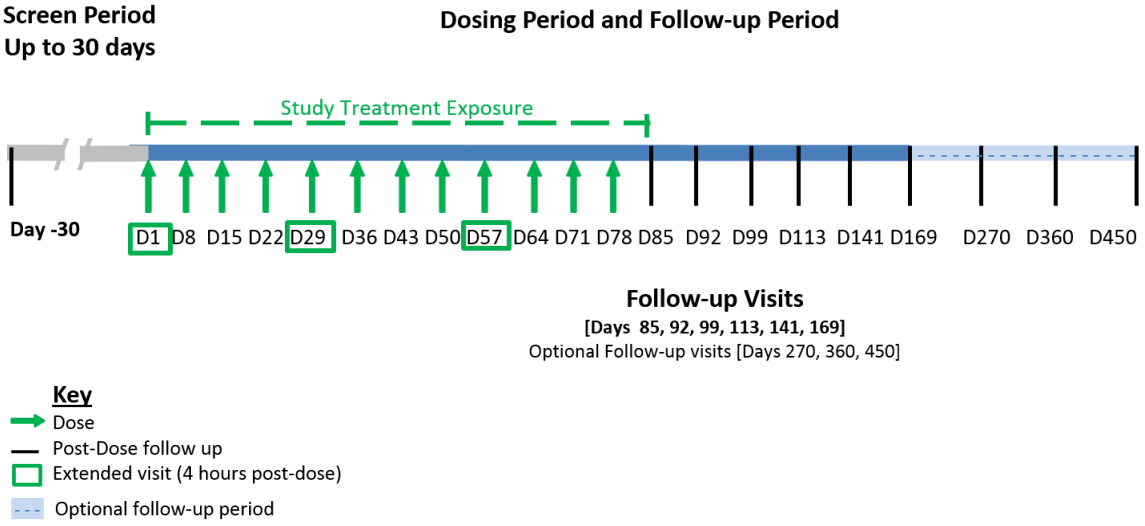
Section 4.2 Treatment Arms and Duration, 4th paragraph
Rationale: To correct the planned study duration

Original text:
In Part 2, the total study duration, including screening, treatment and post-treatment follow-up, is not expected to exceed 65 weeks for each subject (Figure 4 and Figure 5).

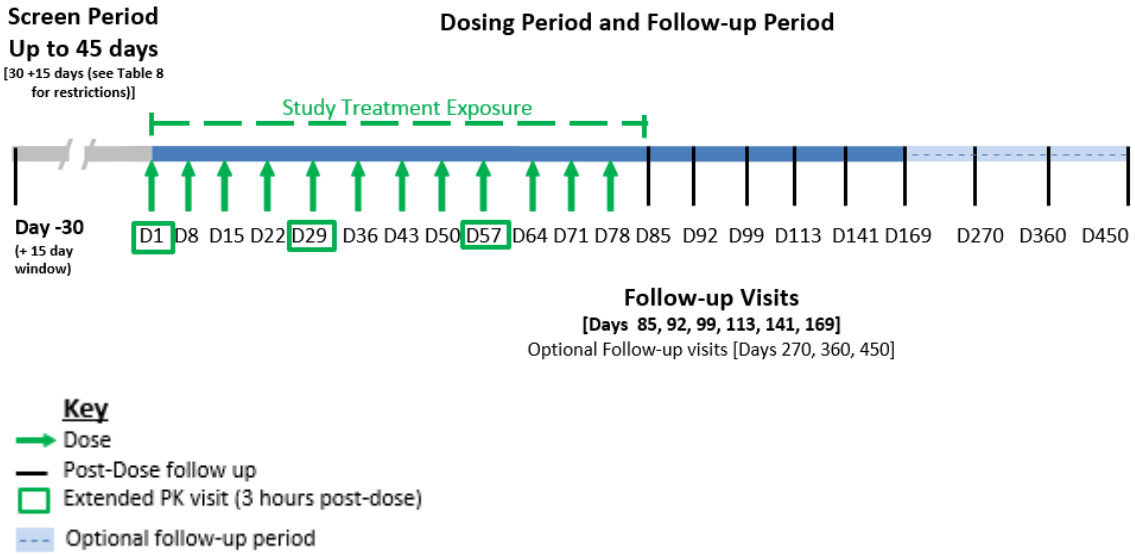
Amended text:
In Part 2, the total study duration, including screening, **(and the 15 day window exceeding the normal 30 day screening window)**, treatment and post-treatment follow-up, is not expected to exceed ~~65~~**71** weeks for each subject (Figure 4 and Figure 5).

Section 4.2 Treatment Arms and Duration, Figure 4
Rationale: To correct the planned study duration (please note that the figure was amended, but a 'strike-through' figure was not included in the amended text)

Original text:

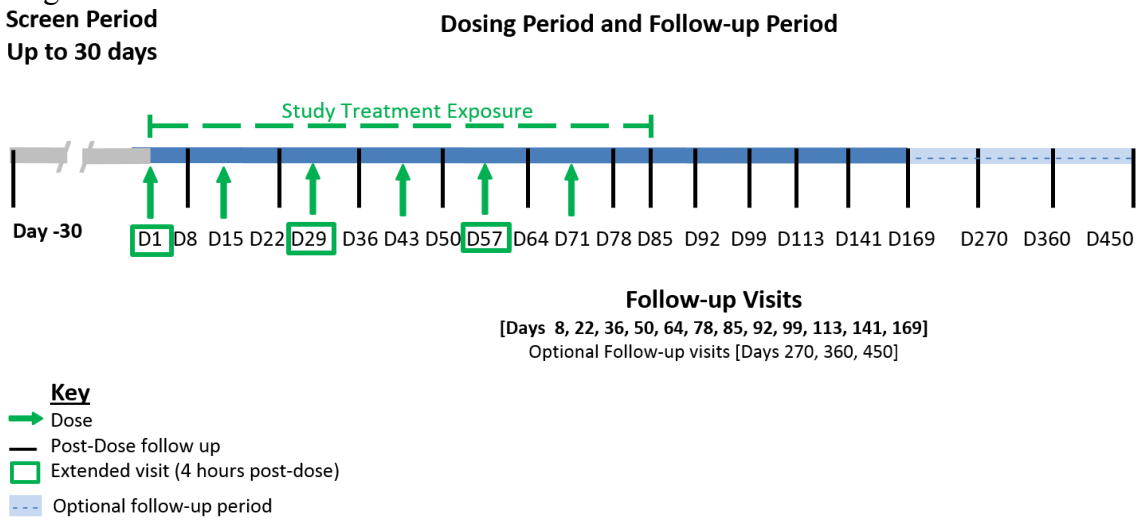


Amended text:

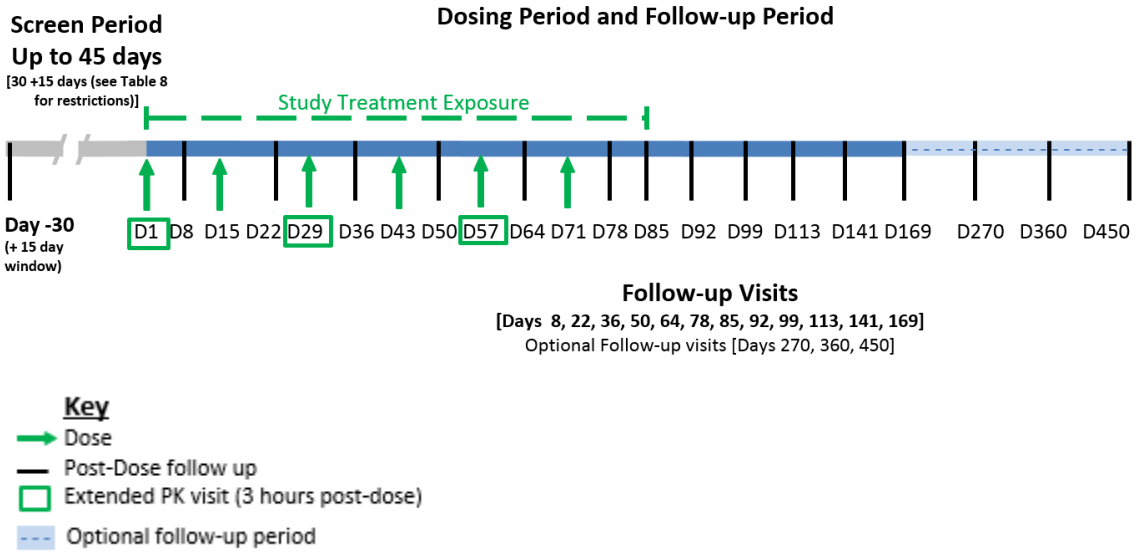


Section 4.2 Treatment Arms and Duration, Figure 5
Rationale: To correct the planned study duration (please note that the figure was amended, but a 'strike-through' figure was not included in the amended text)

Original text:



Amended text:



Section 4.3 Type and Number of Subjects, 1st paragraph, last sentence
Rationale: To provide clarity- to allow for possibility that sites may not be able to recruit HBeAg-positive or negative subjects

Original text:
For Part 2, both HBeAg-positive and HBeAg-negative subjects will be enrolled.

Amended text:
For Part 2, both HBeAg-positive and/**or** HBeAg-negative subjects will be enrolled.

Section 4.3 Type and Number of Subjects, 2nd paragraph, 1st bullet
Rationale: To make edits for clarity- to make clear that 12 subjects were enrolled for the completed Part 1 of study 205670

Original text:

- In Part 1, approximately 20 to 40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol. Twelve subjects were enrolled for part 1 and Part 1 has completed enrollment.

Amended text:

- In Part 1, **twelve subjects were enrolled. Originally** approximately 20 to 40 subjects with CHB were planned for randomization (30 GSK3389404 and 10 placebo under older protocol versions versus 15 GSK3389404 and 5 placebo under amendment 3). A range was provided because different countries and sites may have enrolled under the older versions of the protocol. ~~Twelve subjects were enrolled for part 1 and Part 1 has completed enrollment.~~

Section 4.3 Type and Number of Subjects, 2nd paragraph, 2nd bullet
Rationale: To make edits for clarity- the deleted section was a clerical error that should have been deleted in the previous amendment

Original text:

- In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. Enrolling approximately 39 subjects will ensure enough power for Part 2 with or without the optional Japanese Part 2 sub-study and allow for an approximate a overall drop-out rate, so that there are 11 subjects in each active treatment group and 6 subjects in placebo without the optional Japanese Part 2 sub-study for the primary analysis.

Amended text:

- In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. There are approximately 11 subjects in each of the active treatment groups and approximately 6 subjects in the placebo group.
-
- In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment. ~~Enrolling approximately 39 subjects will ensure enough power for Part 2 with or without the optional Japanese Part 2 sub-study and allow for an approximate a overall drop-out rate, so that t~~**T**here are **approximately** 11 subjects in each active **of the active** treatment group**s** and 6 subjects in placebo~~ without the optional Japanese Part 2 sub-study for the primary analysis~~.

Section 4.5.4 Dose Escalation Justification, 1st paragraph
Rationale: To make edits for clarity- to correct the units of the NOAEL in the 13- and 39-week monkey toxicity study. This does not affect the Cmax/AUC calculations for the NOAEL

Original text:

- the NOAEL of 30 mg/kg/day in the 13-week monkey toxicity study (C_{max} = 52.7 µg/mL; $AUC_{(0-\infty)}$ = 492.7 µg•h/mL) and
- the NOAEL of 2 mg/kg/day in the 39-week monkey toxicity study (C_{max} = 2.9 µg/mL; $AUC_{(0-\infty)}$ = 13.5 µg•h/mL).

Amended text:

- the NOAEL of 30 mg/kg/~~day~~**week** in the 13-week monkey toxicity study (C_{max} = 52.7 µg/mL; $AUC_{(0-\infty)}$ = 492.7 µg•h/mL) and
- the NOAEL of 2 mg/kg/~~ day~~**week** in the 39-week monkey toxicity study (**gender averaged;** C_{max} = 2.9 µg/mL; $AUC_{(0-\tau)}$ = 13.5 µg•h/mL).

Section 4.6.1 Risk Assessment, Table 4, Liver Effects, Impact-eligibility criteria, 2nd paragraph
Rationale: To make edits for clarity

Original text:
Subjects with liver cirrhosis or evidence of cirrhosis (Section 5.2, exclusion criterion 4

Amended text:
Subjects with liver cirrhosis or evidence of cirrhosis **are excluded** (Section 5.2, exclusion criterion 4

Section 4.6.1 Risk Assessment, Table 4, Coagulation Effects, Potential Risk/Summary of Data, last paragraph
Rationale: To make edits for clarity- typo

Original text:
In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, there was no evidence of GSK3389404 related prolongation of aPPT.

Amended text:
In Study 202007, the GSK 3389404 Phase 1 study in healthy subjects, there was no evidence of GSK3389404 related prolongation of ~~aPPT~~**aPTT**.

Section 4.6.1 Risk Assessment, Table 4, Kidney Effects, Impact- Eligibility Criteria 2nd paragraph, last sentence
Rationale: To add greater clarity for exclusion criteria- ACR unit

Original text:
Subjects with serum creatinine >ULN, glomerular filtration rate (GFR) <90 mL/min (but ≥ 60 ml/min may be considered after consultation with the GSK medical monitor), or urine albumin to creatinine ratio (ACR) ≥ 0.03 mg/mg are excluded (Section 5.2, exclusion criteria 8e, 8f, and 8g).

Amended text:
Subjects with serum creatinine >ULN, glomerular filtration rate (GFR) <90 mL/min (but ≥ 60 ml/min may be considered after consultation with the GSK medical monitor), or urine albumin to creatinine ratio (ACR) ≥ 0.03 mg/mg (**or ≥ 30 mg/g**) are excluded (Section 5.2, exclusion criteria 8e, 8f, and 8g).

Section 4.6.1 Risk Assessment, Table 4, Kidney Effects, Strategy, Stopping Criteria, 1st bullet point
Rationale: To add greater clarity for exclusion criteria- ACR unit

Original text:
Persistent urine ACR ≥0.03 mg/mg (or ≥30 mg/g). and without alternative cause(s) identified.

Amended text:

• Persistent urine ACR ≥ 0.03 mg/mg (or ≥30 mg/g). and without alternative cause(s) identified.

Section 4.6.2 Benefit Risk Summary, #7
Rationale: To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period)

Original text:
7. In Part 2, subjects are seen at the clinic on a weekly basis and safety assessments (AE/serious adverse event [SAE] review, physical exam, vital signs, ECG assessments) and comprehensive laboratory testing subjects is performed on a weekly or bi-weekly (every 2 weeks) basis. At the end of the 3-month treatment exposure period, subjects have follow-up to 12 weeks to assess safety with an optional extended follow up to 48 weeks.

Amended text:
7. In Part 2, subjects are seen at the clinic on a weekly basis and safety assessments (AE/serious adverse event [SAE] review, physical exam, vital signs, ECG assessments) and comprehensive laboratory testing subjects is performed on a weekly or bi-weekly (every 2 weeks) basis. At the end of the 3-month treatment exposure period, subjects **will continue to** have **regular assessments during the post treatment** follow-up **period** ~~to 12 weeks to assess safety with an optional extended follow up to 48 weeks~~.

Section 5.1 Inclusion Criteria, #9b
Rationale: After feedback from investigators, the inclusion criterion 9b was changed to allow ALT ≤ 2XULN. This change was supported by feedback that factors other than HBV may contribute to slightly elevated ALT levels in subjects

Original text:
b. ALT ≤ ULN for subjects who are receiving stable nucleos(t)ide analogue therapy

Amended text:
b. ALT ≤ **2 X** ULN for subjects who are receiving stable nucleos(t)ide analogue therapy

Section 5.2 Exclusion Criteria, #4d
Rationale: to add greater clarity- after feedback from investigators, the exclusion criterion 4 was edited to include exclusion of subjects who the investigator believes may have liver cirrhosis without requiring a positive liver biopsy, Fibroscan, and/or APRI/Fibrosure result to exclude the subject

Original text:
N/A

Amended text:

d. investigator judgmenet

Section 5.2 Exclusion Criteria, #8g
Rationale: to add greater clarity- sites may use an online calculator that converts the ACR to mg/g instead of mg/mg and to clarify situations where subjects have both low urine albumin and low urine creatinine

Original text:

g. Urine albumin to creatinine ratio (ACR) ≥0.03 mg/mg. In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement

Amended text:

g. Urine albumin to creatinine ratio (ACR) ≥0.03 mg/mg **(or ≥ 30 mg/g).** In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement

i. **In cases where subjects 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 patient does not have a history of diabetes, hypertension or other risk factors that may affect renal function and discuss with the PPD or GSK medical monitor, or designee**

Section 5.2 Exclusion Criteria, #10
Rationale: to add greater clarity

Original text:
10.Fridericia's QT correction formula (QTcF) ≥450 msec (mean of triplicate measurements).

Amended text:
10. 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 subject meets exclusion criterion**).

Section 5.2 Exclusion Criteria, #11
Rationale: to add greater clarity- some subjects use topical or inhaled corticosteroids, which would not result in the immunosuppressing effects

Original text:
11. Currently taking, or took within 3 months of screening, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks)

Amended text:

11. Currently taking, or took within 3 months of screening, any immunosuppressing drugs (e.g., prednisone), other than a short course of therapy (≤2 weeks) **or topical/inhaled steroid use**

Section 5.2 Exclusion Criteria, #13
Rationale: to make clear that this exclusion criteria is in reference to illicit drug/substance dependency

Original text:

13. A positive pre-study treatment screen or an unwillingness to refrain from use of the illicit drugs and adhere to other protocol-stated restrictions while participating in the study.

Amended text:

13. A positive pre-study treatment screen **and** ~~or~~ an unwillingness to refrain from use of ~~the~~ illicit drugs **(or substances with abuse potential)** and adhere to other protocol-stated restrictions while participating in the study. **[The screen refers to illicit drugs and substances with abuse potential. Medications that are used by the patient as directed, whether over-the-counter or through prescription, are acceptable and would not meet the exclusion criteria]**

Section 5.4 Withdrawal/Stopping Criteria, 1st paragraph
Rationale: To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

Original text:
Subjects who are discontinued from study treatment will enter the post-treatment follow-up period unless consent is withdrawn.

Amended text:
Subjects who are discontinued from study treatment will enter the post-treatment follow-up period (**please submit an electronic protocol inquiry platform [EPIP] query (either site or clinical research associate [CRA] may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment) unless consent is withdrawn.**

Section 5.4.1 Liver Chemistry Stoping Criteria, 3rd paragraph, 1st sentence
Rationale: For clarity, to align with changes in ALT criteria

Original text:
Eligible subjects in Part 1 may have an elevated ALT at screening as specified in Section 5.1.

Amended text:
Eligible subjects in Part 1 **and Part 2** may have an elevated ALT at screening as specified in Section 5.1.

Section 5.4.1 Liver Chemistry Stoping Criteria, 4th paragraph, last sentence
Rationale: To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

Original text:
The subject must then attend the Follow-up visits specified in the Time and Events Table

Amended text:
~~The subject must then attend the Follow-up visits specified in the Time and Events Table~~
Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment

Section 5.4.2 QTc Stopping criteria, last sentence
Rationale: To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

Original text:
If a single ECG measurement demonstrates a prolonged QTcF interval, the ECG should be repeated 2 more times and the average of the 3 QTcF values used to determine whether the subject should be discontinued from the study.

Amended text:
Discontinuation of subjects will be based on average QTcF from triplicate ECGs. If a single ECG measurement demonstrates a prolonged QTcF interval, the ECG should be repeated 2 more times and the average of the 3 QTcF values used to determine whether the subject should be discontinued from the study **treatment. Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment**

Section 5.4.3 Hematological Stopping Criteria last sentence
Rationale: To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

Original text:
N/A

Amended text:
Please submit an EPIP query (either site or CRA may submit) to receive post-treatment follow up dates for subjects who discontinue study treatment
Section 5.4.4 Renal Stopping Criteria, 1st bullet point
Rationale: To provide greater clarity on exclusion criteria- ACR units

Original text:
- Persistent urine ACR ≥0.03 mg/mg and without alternative cause(s) identified

Amended text:
- Persistent urine ACR ≥0.03 mg/mg **(≥30 mg/g)** and without alternative cause(s) identified

Section 5.4.5 Pharmacokinetic Stopping Criteria, 1st paragraph
Rationale: to make edits for clarity- to correct the units of the NOAEL in the 13-week monkey toxicity study were written as the NOAEL of 30 mg/kg/day, when it should be mg/kg/week

Original text:
Part 1: Doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma AUC(0-∞) and Cmax observed at the NOAEL dose of 30 mg/kg/day in the 13 week monkey toxicity study (AUC(0 ∞) = 492.7 mg•h/mL and Cmax = 52.7 mg/mL).

Amended text:
Part 1: Doses will be escalated such that the predicted mean plasma exposure at the next dose level will not exceed the mean plasma AUC(0-∞) and Cmax observed at the NOAEL dose of 30 mg/kg/~~day~~**week** in the 13 week monkey toxicity study (AUC(0-∞) = 492.7 mg•h/mL and Cmax = 52.7 mg/mL).

Section 6.1 Investigational Product and Other Study Treatment, Table 6
Rationale: To make edits for clarity- for consistency with other sections/source document wording
Original text:

Unit Dose Strength(s)/Dosage Level(s):	100 mg/mL; 1.0 mL nominal volume per vial (0.25 mL overfill per vial)	Placebo

Amended text:

Unit Dose Strength(s)/Dosage Level(s):	100 mg/mL; 1.0 mL nominal volume per vial (~~0.25mL~~ **minimal** overfill per vial)	Placebo

Section 6.1 Investigational Product and Other Study Treatment, Table 6
Rationale: to make edits for clarity- to remove the word “pharmacy” for dispensing investigational product (IP; GSK3389404 or placebo), not all sites use a formal pharmacy to dispense IP

Original text:

Method for Individualizing Dosage:	Dispensing into syringes in pharmacy	Dispensing into syringes in pharmacy

Amended text:

Method for Individualizing Dosage:	Dispensing into syringes ~~in pharmacy~~	Dispensing into syringes ~~in pharmacy~~

Section 6.5 Blinding, 4th bullet
Rationale: To update the unblinded senior management review

Original text:

- Management review of unblinded efficacy data is planned for both parts of the study. For part 1, the review provides early information on potential efficacious dose and dose frequency including the need for dose escalation. For part 2, the review will facilitate internal governance decision making on project progress and trigger futher studies. Unblinded efficacy data may be provided to the following management/function as required: Senior VP of Infectious Disease Therapy Area, Head Unit Physician, Project Statistician, Head of ID Statistics/Programming, Director of Clinical Pharmacology, Safety Evaluation and Risk Management, Global Regulatory Lead, Project Physician Lead, Clinical Investigator Lead, Clinical Development Manager,Global Marketing Director

Amended text:

- **Senior m**anagement review of unblinded efficacy data is planned for both parts of the study (**this includes the Japanese optional sub-study**). For part 1, the review provides early information on potential efficacious dose and dose frequency including the need for dose escalation. For part 2, the review will facilitate internal governance decision making on project progress and trigger futher studies. ~~Unblinded efficacy data may be provided to the following management/function as required: Senior VP of Infectious Disease Therapy Area, Head Unit Physician, Project Statistician, Head of ID Statistics/Programming, Director of Clinical Pharmacology, Safety Evaluation and Risk Management, Global Regulatory Lead, Project Physician Lead, Clinical Investigator Lead, Clinical Development Manager,Global Marketing Director~~

Section 6.5 Blinding, 5th bullet
Rationale: To update the unblinded senior management review

Original text:

• The frequency of management review in Part 2 will be synchronized with monthly blinded SRT review of the study. The management review of the Part 1 data will occur as required for decision making.

Amended text:

- The frequency of management review in Part 2 will be synchronized with monthly blinded SRT review of the study **as appropriate**. The management review of the Part ~~1~~**2** data will occur as required for decision making.

Section 6.12.1 Permitted Medications and Non-Drug Therapies, 3rd paragraph
Rationale: To make edits for clarity
Original text:
N/A

Amended text:
If patients are receiving nucleos(t)ide therapy, administration of the nucleos(t)ide should continue unchanged unless directed by the physician. There are no requirements with regards to the timing of the administration of nucleos(t)ide agent in relation to the study medicine.

Section 6.12.1 Permitted Medications and Non-Drug Therapies, 5th paragraph
Rationale: To make edits for clarity

Original text:
Traditional Chinese medicine (TCM) and/or acupuncture should be avoided during the duration of the study. However, if subjects report use of TCM and/or acupuncture, then details must be recorded in the concomitant medication CRF.

Amended text:
Traditional Chinese medicine (TCM) and/or acupuncture **as it relates to CHB therapy** should be avoided during the duration of the study. ~~However,~~ If subjects report use of TCM and/or acupuncture, then details must be recorded in the concomitant medication CRF.

Section 6.12.2 Prohibited Medications and Non-Drug Therapies, 1st sentence
Rationale: To make edits for clarity

Original text:
The following concomitant medications are not permitted during Part 1 and Part 2

Amended text:
The following concomitant medications are not permitted during Part 1 and Part 2 **(until Day 169 unless indicated otherwise)**

Section 6.12.2 Prohibited Medications and Non-Drug Therapies, 3rd bullet
Rationale: To make edits for clarity

Original text:
- Non-GSK -oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit or prior treatment with a GSK oligonucleotide from 3 months

prior to Day 1 through the final Follow-up visit (see Exclusion Criterion 16, Section 5.2).

Amended text:

- Non-GSK -oligonucleotide or siRNA from 12 months prior to Day 1 through the final Follow-up visit or prior treatment with a GSK oligonucleotide from 3 months prior to Day 1 through the final Follow-up visit (**includes optional follow-up period if applicable;** see Exclusion Criterion 16, Section 5.2).

Section 7.1 Time and Events Table, Table 8

Rationale: To correct the planned study duration for the subjects- it did not include the screening window period of 30 days (+15 days exceeding the 30 day screening window) ; (please note for table, only sections effected will be shown, not the whole table)

Original text:

Assessment	**Screening (Up to 30 days Prior to Day 1)**

Amended text:

Assessment	**Screening (Up to 30 days Prior to Day 1)***

*** Eligible subjects who exceed the regular 30-day screening window by 15 days (total 45 days) should undergo a brief physical exam, review of medical history, and review of concomitant medications to confirm eligibility**

Section 7.1 Time and Events Table, Footnote 3 (Table 11 and 13) or Footnote 1 (Table 12, 14, and 15)

Rationale: To provide clarity

Original text:

Footnote. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Amended text:

Footnote. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs**, including those** assessed as related to study participation (e.g., protocol mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).

Section 7.1 Time and Events Table, Table 11 and Table 13

Rationale: To make edits for clarity- to make clear that only subjects of reproductive potential should undergo pregnancy testing; (please note for table, only sections effected will be shown, not the whole table)

Original text:
Footnote 8. Female subjects at screening: serum hCG pregnancy test; all other time points serum hCG or urine pregnancy test. (Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)

Amended text:
Footnote 8. Female subjects at screening: serum hCG pregnancy test; all other time points **for females of reproductive potential**: serum hCG or urine pregnancy test. (Confirm subject is not pregnant with either serum hCG or urine pregnancy test prior to dosing.)

Section 7.1 Time and Events Table, Table 15
Rationale: to update the Time and Events Table for the optional follow-up period

Original text:

	Day 270 (±7 days)	**Day 360 (±7 days)**	**Day 450 (±7 days)**	**ET**
Outpatient visit	X	X	X	X
Safety Assessments				
AE/SAE review[1]	← Continuous →			X
Concomitant medication review	← Continuous →			X
Brief physical exam	X	X	X	X
Vital signs[2]	X	X	X	X
Laboratory Assessments[4]				
Pregnancy test (as appropriate)[5]			X	X
Hematology/Chemistry/Urinalysis[6]	X	X	X	X
Urine ACR[5,6]	X	X	X	X
Complement (C3/C4)	X	X	X	X
PT, INR, aPTT	X	X	X	X
hs-CRP	X	X	X	X
Archived serum and plasma samples[7]	X	X	X	X
HBsAg and HBV DNA	X	X	X	X
HBeAg[8]	X	X	X	X
HBV genotype/phenotype[9]	X	X	X	X
HBsAb	X	X	X	X
Meal[10]	X	X	X	X

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).
3. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments.
4. Female subjects of reproductive potential: serum hCG or urine pregnancy test.
5. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessment.

6. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.
7. Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
8. HBeAg-positive subjects only.
9. HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
10. Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Amended text:

	Day 270 (±7 days)	**Day 360 (±7 days)**	**Day 450 (±7 days)**	**ET**
Outpatient visit	X	X	X	X
Safety Assessments				
AE/SAE review[1]	← Continuous →			X
Concomitant medication review	← Continuous →			X
~~Brief physical exam~~	~~X~~	~~X~~	~~X~~	~~X~~
~~Vital signs~~[2]	~~X~~	~~X~~	~~X~~	~~X~~
Laboratory Assessments[4]				
~~Pregnancy test (as appropriate)~~[5]			~~X~~	~~X~~
~~Hematology~~/Chemistry/~~Urinalysis~~[6]	X	X	X	X
~~Urine ACR~~[5,6]	~~X~~	~~X~~	~~X~~	~~X~~
~~Complement (C3/C4)~~	~~X~~	~~X~~	~~X~~	~~X~~
PT, INR,~~ aPTT~~	X	X	X	X
~~hs-CRP~~	~~X~~	~~X~~	~~X~~	~~X~~
Archived serum and plasma samples~~7~~**2**	X	X	X	X
HBsAg and HBV DNA	X	X	X	X
HBeAg~~8~~**3**	X	X	X	X
HBV genotype/phenotype~~9~~**4**	X	X	X	X
HBsAb	X	X	X	X
Meal~~10~~**5**	X	X	X	X

1. Adverse events will be collected from the time of first dose of study treatment and until the final Follow-up visit. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) or related to GSK3389404 will be recorded from the time a subject consents to participate in the study up to and including any Follow-up visit. All AEs and SAEs will be graded based on the DAIDS table or supplemental criteria as defined in Appendix 3 (Section 12.3.5.1).
~~2. Temperature and respiration rate (single measurement); blood pressure and heart rate (single measurement after 5 minutes of rest in the semi-supine or supine position).~~
~~3. Samples for clinical laboratory tests to be collected after vital sign and ECG assessments.~~
~~4. Female subjects of reproductive potential: serum hCG or urine pregnancy test.~~
~~5. The study site may collect and divide urine sample for urinalysis test and ACR (first void) assessment.~~
~~6. Collect first morning urine void sample for ACR assessment. For outpatient visits, subjects will be given a clean urine collection cup and instructed to collect and bring in a first morning urine void sample on the day of their outpatient visit.~~
~~7~~**2.** Archived serum and plasma samples for exploratory biomarker analyses. Complement C5a and Bb as well as HBV RNA, HBcrAg, and/or IDO may be analyzed from the archived samples.
~~8~~**3.** HBeAg-positive subjects only.

~~9~~**4.** HBV genotype/phenotype samples to be stored and analyzed per sponsor's discretion. Samples will be used to assess for changes in HBV genotype/phenotype from baseline, HBsAg nadir, and/or final Follow-up visit.
~~10~~**5.**Subjects will be offered a meal (e.g., bagged or canteen [or reimbursed]) after completion of all study procedures.

Section 7.3.1.1 Time Period and Frequency for Collecting AE and SAE information, 1st bullet
Rationale: To provide clarity

Original text:
• Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Amended text:
• Any SAEs, **including those** assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Section 7.3.1.3 Follow-up of AEs and SAEs
Rationale: To provide next steps for determining follow-up visit schedules for subjects who meet treatment stopping criteria, but are not withdrawn from the study

Original text:
After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3 (Section 12.3.5.4).

Amended text:
After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). **After the SAE or AE are followed until resolution or stabilization or event is otherwise explained, the subject will enter into the post-treatment follow up. The exact schedule for post-treatment follow up for those subjects who withdraw study treatment early should be confirmed with the GSK team.** Further information on follow-up procedures is given in Appendix 3 (Section 12.3.5.4).

Section 7.3.2 Pregnancy, 1st bullet

Rationale: To provide clarity- To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period)

Original text:

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until the final specified Follow-up visit

Amended text:

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until the final specified Follow-up visit **(includes the optional follow-up period for Part 2).**

Section 7.3.7 Clinical Safety Laboratory Assessments, 2nd bullet
Rationale: to clarify that China may also use local laboratory result (urine drug test) for screening as it is not available at the China central laboratory

Original text:
N/A
Amended text:

- **For China, urine drug screen. The results of each test must be entered into the CRF.**

Section 7.3.7 Protocol Required Safety Laboratory Assessments, Table 16, Other screening and/or follow-up tests
Rationale: To provide edits for clarity- genotype/phenotype testing is separate from HBeAg testing

Original text:

- Viral genotype HBeAg positive or HBeAg negative

Amended text:

- Viral genotype**/phenotype**
- HBeAg ~~positive or HBeAg negative~~)

Section 12.1 Appendix 1 Abbreviations
Rationale: To make edits for clarity

Original text:
N/A

Amended text:

CRA	**Clinical Research Associate**
EPIP	**Electronic Protocol Inquiry Platform**

Section 12.3.5.3 Toxicity Management, Anemia, Grade 2
Rationale: Edits for clarity-

Original text:

1. peripheral blood smear
10. indirect bilirubin (abnormal if increased > 50% from baseline)
11. haptoglobin (abnormal if ≤ 25 mg/dL)
12. reticulocyte count (abnormal if ≥ 4%)

Amended text:

1. peripheral blood smear
~~10~~**2**. indirect bilirubin (abnormal if increased > 50% from baseline)
~~11~~**3**. haptoglobin (abnormal if ≤ 25 mg/dL)
~~12~~**4**. reticulocyte count (abnormal if ≥ 4%)

Section 12.4.1, 1st paragraph, last sentence
Rationale: To differentiate between final follow up visits Day 169 or Day 450 (if subjects consent to the optional extended follow-up period)

Original text:
Male subjects with female partners of child bearing potential and female subjects of child bearing potential must comply with the following contraception requirements from either the time of first dose of study treatment (male) or from at least 28 days prior to the first dose of study treatment (FRP) until the final Follow-up visit.

Amended text:
Male subjects with female partners of child bearing potential and female subjects of child bearing potential must comply with the following contraception requirements from either the time of first dose of study treatment (male) or from at least 28 days prior to the first dose of study treatment (FRP) until ~~the final~~ Follow-up visit **Day 169**.

Section 12.6.5 Simulations, 3rd paragraph
Rationale: To make edits for clarity

Original text:
Simulation results for all scenarios are summarized in Table 19 toTable 27

Amended text:
Simulation results for all scenarios are summarized in Table 19 to Table ~~27~~**22**

Section 12.6.5 Simulations, Table 20
Rationale: To make edits for clarity

Original text:

Scenario 2

Treatment	Posterior RR (%)
PBO	6.82
240W	30.93
240BM	30.09
480W	30
PBO	6.95
240W	30.38
240BW	29.88
480W	29.77

Amended text:

	Scenario 2	
	Treatment	Posterior RR (%)
Pairwise		
	PBO	6.82
	240W	30.93
	240BM	30.09
	480W	30
BLRM	PBO	6.95
	240W	30.38
	240BW	29.88
	480W	29.77