Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 205670: 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 (Part 2)
Compound Number	:	GSK3389404
Effective Date	:	19-NOV-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205670: 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 (Part 2).

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Part 2 of Protocol 205670:

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.		

GlaxoSmithKline Document Number	Date	Version
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-13	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 Events Table for the optional follow-up period. To update the unblinded 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 edits for clarity		

Overview	Key Elements of the RAP
Purpose	• This reporting and analysis plan (RAP) details planned analyses for Part 2 of a clinical study report for study 205670 which will be used to support the regulatory submissions for the treatment of subjects with chronic Hepatitis B (CHB).
Protocol	• This RAP is based on the protocol amendment number 6 [(Dated: 2018-JUN-13) of study 205670 (GSK Document No.: 2016N277028_07)].
Primary Objectives	• To assess the safety, tolerability, and PK profile of GSK3389404 in multiple (Part 2) administration in subjects with CHB. • To identify one or more efficacious dose(s) and dosing regimen(s) of GSK3389404 over a planned duration of 3 months (Part 2).

Primary Endpoints	• Safety and Tolerability
	  • As measured by clinical assessments including, but not limited to
	  • Vital signs
	  • Physical examinations
	  • 12-lead electrocardiograms (ECGs)
	  • Laboratory measurements (hematology, clinical chemistry, coagulation parameters, complement and urinalysis)
	  • Adverse events (AEs), serious adverse events (SAEs), discontinuations

Overview	Key Elements of the RAP
	• 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 (part 2).

Secondary Endpoint	• Pharmacodynamic:
	  • 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).
	• Pharmacokinetic:
	  • GSK3389404 and ISIS 505358 plasma concentrations (Part 2).
	  • Derived GSK3389404 and ISIS 505358 plasma PK parameters for Japan-enrolled Japanese sub-study (JSS) subjects 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).

Study Design	• Part 2 will be conducted as a randomized, double-blind, placebo-controlled, multiple-dose, dose-ranging study. Subjects will be randomized to the following dose levels and regimens or placebo. The dose levels and regimens for Part 2 are 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 480 mg.
	  ○ 60 mg at weekly
	  ○ 120 mg at bi-weekly
	  ○ 120 mg at weekly
	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 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.
	• A Japanese sub-study was included in Part 2. Subjects will be randomized to the following dose levels and regimens or placebo.

Overview	Key Elements of the RAP
	○ 30mg at weekly ○ 60 mg at weekly ○ 120 mg at bi-weekly ○ 120 mg at weekly • 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.
Planned Analyses	• 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. • 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 450 visit.
Analysis Populations	• All Subjects Screened Population • Safety Population • Pharmacokinetic Population • Pharmacodynamic Population • Intent-to-Treat (ITT) Population
Hypothesis	• 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 95%), i.e. $P(RR_{ACT} > RR_{PBO}) \geq 90\%$, 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.
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.

Overview	Key Elements of the RAP

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

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.
	• Pharmacokinetics (ISIS 505358)
	  • 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 PK parameters for the Japan-enrolled JSS subjects 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.

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

Overview	Key Elements of the RAP
	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.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the planned statistical analysis specified in the protocol [(Dated: 2018-JUN-13)].

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety, tolerability, and PK profile of GSK3389404 in multiple (Part 2) administration in subjects with CHB.	• Safety and Tolerability As measured by clinical assessments including, but not limited to o Vital signs o Physical examinations o 12-lead electrocardiograms (ECGs) o Laboratory measurements (e.g., chemistry, hematology) o 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 Objectives	**Secondary Endpoints**
• To assess the PD effect of GSK3389404 in subjects with CHB (Part 2).	• Correlation between GSK3389404 PK parameters and PD parameters, including HBV 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, following single and multiple dose administration of GSK3389404 (Part 2).	• Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (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 patients, defined as presence of HBV surface antibody (HBsAb) (Part 2 only)	• Rate of seroconversion

2.3. Study Design

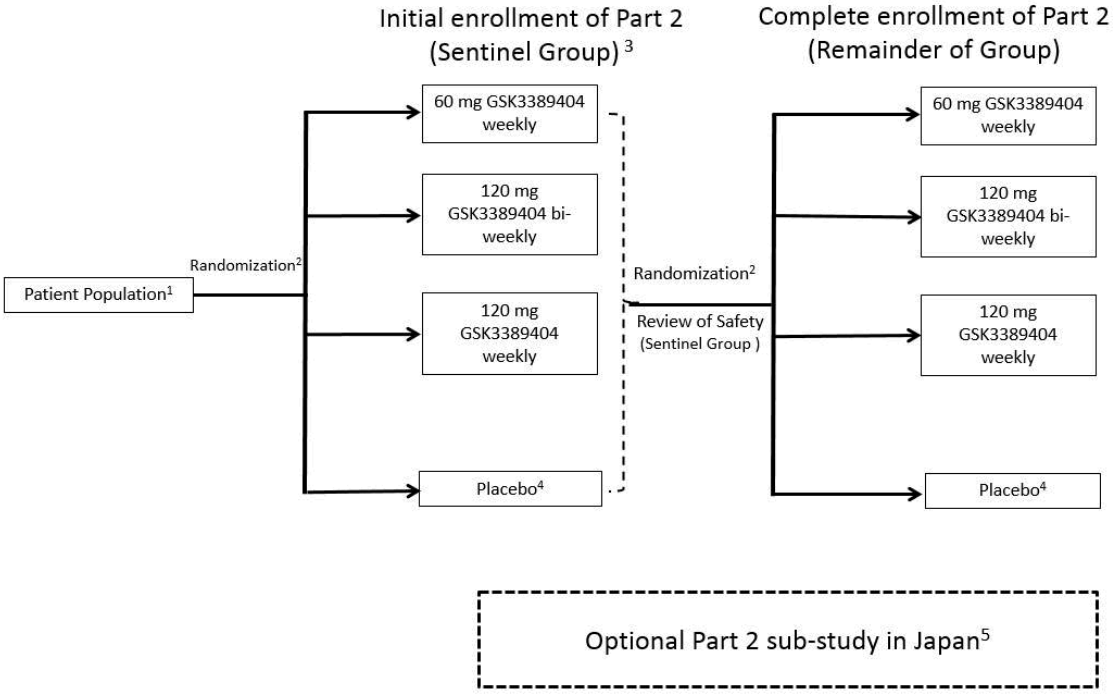
Overview of Study Design and Key Features

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 2 will be conducted as a multiple-dose, dose-ranging 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 following dose levels and regimens are selected for Part 2 main study:
  - 60 mg at weekly
  - 120 mg at bi-weekly
  - 120 mg at weekly
- The following dose levels and regimens are selected for Part 2 Japanese sub-study (JSS):
  - 30 mg at weekly
  - 60 mg at weekly
  - 120 mg at bi-weekly
  - 120 mg at weekly

Figure 1 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.

Overview of Study Design and Key Features	
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.	

Dosing	Part 2, Multiple Dose and Dose ranging:
	• The dose levels and regimens for Part 2 will be selected after a review of Part 1 safety, but will not exceed a total monthly dose of 480 mg.
	• The following dose levels and regimens are selected for Part 2 main study:
	  ○ 60 mg at weekly
	  ○ 120 mg at bi-weekly
	  ○ 120 mg at weekly
	• The following dose levels and regimens are selected for Part 2 Japanese sub-study (JSS):
	  ○ 30 mg at weekly
	  ○ 60 mg at weekly
	  ○ 120 mg at bi-weekly
	  ○ 120 mg at weekly

Treatment Assignment	Separate randomization schedules will be generated for each part of the study (Part 2 Sentinel, Part 2 Remainder, Part 2 JSS). Part 2: • Sentinel group ratio: 1:1 for each active treatment group and the corresponding matching placebo • 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). • JSS will have separate randomization ratio
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. • If applicable, the analysis of the Japanese 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 sub-study will be unblinded. The analysis will be reported together with the Primary analysis. • The 3 month follow up analysis for Part 2 will be conducted once last randomized subject has completed the Day 169 visit.

Overview of Study Design and Key Features	
	• 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.
Rules for Safety Concern	Part 2: • A sentinel group will be dosed first. • Safety data from 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 the review of safety data from at least 2 weeks of exposure in the all sentinel group subjects.
Type and Number of Subjects	• Adult male and female subjects with CHB between18 and 70 years of age, inclusive, and not currently receiving CHB treatment are planned for inclusion. • In Part 2, approximately 39 subjects with CHB are planned for randomization to study treatment for the main study. • If Japan participates in the optional Japanese Part 2 sub-study, approximately 22 subjects may be enrolled.

2.4. Statistical Hypotheses

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 copies/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 the active group, RR_{PBO} is the RR in the placebo group, and P is the posterior probability.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analysis is planned for Part 2. Safety data from a sentinel group will be reviewed by the GSK internal clinical team or Safety review team (SRT) in a blinded manner. 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 including a review when all subjects completed Day 28 visit.

A unblinded review of efficacy and safety is planned for project decision. The details of unblinded reviewed are included in the unblinded review charter.

3.2. Final Analyses

For below analysis, two sets of TLFs will be provided. There will be

- TLFs include data from subjects in main study and JSS (all subjects)
- TLFs include data from subjects in JSS only (JSS)

3.2.1. 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.

3.2.2. JSS Optional Analysis

The analysis of Japanese cohort will be conducted and reported together with the Primary analysis and 3 month follow up analysis. JSS analysis will be included in 6 month follow up analysis and end of study analysis if number of subjects warrant additional analysis.

3.2.3. 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.

3.2.4. 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.

3.2.5. 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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Screened	• The All Subjects Screened Population will include all subjects who consent to participate in the clinical trial. • The population will be defined separately for all subjects and JSS.	• Screen failure summary.
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study. • The population will be defined separately for all subjects and JSS.	• Study population summary
Safety	• Include all subjects who receive at least one dose of the study treatment (including placebo) • This population will be based on the treatment the subject actually received. • The population will be defined separately for all subjects and JSS.	• Safety
Intent-To-Treat (ITT)	• Comprise of all randomized subjects. • This population will be based on the treatment to which the subject was randomized. • Any subject who receives a treatment randomization number will be considered to have been randomized. • The population will be defined separately for all subjects and JSS.	• Efficacy • Study Population
Pharmacokinetic (PK)	• Include all subjects in the Safety population for whom at least one evaluable PK sample was obtained and analyzed. • PK samples that may be affected by protocol deviations will be reviewed by the study team and determined whether or not the sample will be excluded. • The population will be defined separately for all subjects and JSS	• PK
Pharmacodynamic (PD)	• Include all subjects in the Safety population who provide evaluable PD data.	• PD

Population	Definition / Criteria	Analyses Evaluated
	• The population will be defined separately for all subjects and JSS.JSS	

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions for Part 2 All Subjects and Part 2 Japanese Sub-Study
Data Displays for Reporting
Description
Placebo
GSK3389404 30mg Weekly
GSK3389404 60mg Weekly
GSK3389404 120mg bi-weekly
GSK3389404 120mg Weekly
All Active
Total
Placebo (HBeAg-)
GSK3389404 30mg Weekly (HBeAg-)
GSK3389404 60mg Weekly (HBeAg-)
GSK3389404 120mg Bi-Weekly (HBeAg-)
GSK3389404 120mg Weekly (HBeAg-)
All Active (HBeAg-)
Placebo (HBeAg+)
GSK3389404 30mg Weekly (HBeAg+)
GSK3389404 60mg Weekly (HBeAg+)
GSK3389404 120mg Bi-Weekly(HBeAg+)
GSK3389404 120mg Weekly (HBeAg+)
All Active (HBeAg+)

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the last value/assessment before the first dose of the study treatment (Day 1 pre-dose), including those from unscheduled visits. If there are multiple assessments collected at the same scheduled time (e.g., triplicate 12-lead ECGs), the average of these assessments will be used as the baseline.

Unless otherwise stated, if baseline data is missing, no derivation will be performed and baseline will be set to missing.

For hematology tests collected from local lab, actual time was not collected for Day 1 sample. However with site confirmation that the samples were drawn at the same timing as other blood draw for central lab, the central lab collected time will be used for the local lab records in order to decide if the record is eligible for baseline.

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.

Subgroup	Categories
Baseline HBsAg	<=1000 or > 1000 IU/mL
Race	a. Japanese or Non-Japanese b. Central/South Asian, East Asian, Japanese, South East Asian, Other
Country	China, Japan, South Korea, Hong Kong, Other
Gender	Male, Female
HBeAg Status	Positive or Negative

5.4. Other Considerations for Data Analyses and Data Handling Conventions

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 13.1	Appendix 1: Schedule of Activities
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events

Section	Appendix
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions • Reporting Process • Reporting Standards • Baseline Definition & Derivations
Section 13.5	Appendix 5: Derived and Transformed Data • General • Study Population • Safety • Pharmacokinetic • Pharmacodynamic
Section 13.6	Appendix 6: Reporting Standards for Missing Data for Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance
Section 13.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 13.9	Appendix 9: Abbreviations & Trade Marks
Section 13.10	Appendix 10: List of Data Displays
Section 13.11	Appendix 11: Bayesian Modelling Details

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Randomization			
Randomization			Y
Subject Disposition			
Number of Subjects Enrolled by Country and Site	Y		
Subject Disposition	Y		
Screen Failures	Y		Y
Reason for Withdrawals	Y		

Display Type	Data Displays Generated		
	Table	Figure	Listing
Important Protocol Deviations	Y		Y
Demography			
Demographics	Y		Y
Baseline Disease Characteristics	Y		Y
Race & Racial Combinations	Y		Y
Age Ranges	Y		
Subjects Excluded from Study Populations			Y
Medical Condition & Concomitant Medications			
Past/Current Medical Conditions	Y		Y
Concomitant Medications	Y		Y
Baseline Nucleos(t)ide Use	Y		Y

NOTES :

- Y = Yes display generated.

6.1.1. Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study. In each study part, subject disposition will be tabulated for each study treatment and for all subjects combined with the number of subjects who complete the study, prematurely discontinue, and the reason (primary and secondary, if available) for early discontinuation. Summaries will also be provided for number of subjects enrolled by site, reasons for screen failure and important protocol deviations.

Listings of inclusion/exclusion criteria deviations, reasons for screen failure, early withdrawal, treatment randomization, important protocol deviations and study treatment administration will be provided for each study part.

6.1.2. Demographic and Baseline Characteristics

Individual subject demographics, race and racial combinations, age ranges and subjects excluded from study populations will be presented in listings for each study part.

Demographic characteristics such as age, sex, race, ethnicity, child bearing potential, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment and for all subjects overall for each study part. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percent will be presented for age category, sex, race, ethnicity and child bearing potential.

Other baseline characteristics include but not limited to drug/alcohol use, HIV, HDV and hepatitis C information at screening, quantitative HBsAg and quantitative HBV DNA, HBeAg status [±], HBeAg level, and ALT level [x ULN].

6.1.3. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed for each study part using generic term, verbatim text, and indication. The summary of prior and concomitant medications will show the number and

percentage of subjects taking prior and concomitant medications and corresponding Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information.

Please refer to Appendix 1 for definition of prior, concomitant and post-treatment medications. Handling of partial dates for medications is outlined in Appendix 6: Reporting Standards for Missing Data.

6.1.4. Medical History and Current Medical Conditions

Medical history and current medical conditions will be summarized and display the number and percentage of subjects for each body system.

6.1.5. Treatment Exposure

Treatment exposure will be summarized for Part 2 subjects. Summary includes duration of treatment, the number of doses administered and total volumes of doses. Dose administration for all subjects Part 2 will be displayed in the listing.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

The primary efficacy objective (Part 2 only) is to select an efficacious dose level and dosing regimen of GSK3389404 as determined by the primary endpoint RR.

7.1.1. Endpoint / Variables

The primary efficacy analyses endpoint is response rate (RR) where response is based on reduction of HBsAg level from baseline. A subject will be considered a responder if there is at least 1.5 log 10 IU/mL reduction of HBsAg levels from baseline (i.e., less or equal to $10^{-1.5}$ (or 3.16%) of baseline value) anytime during the study. If subject has no post-baseline assessment of HBsAg levels, subject will be considered a non-responder.

For different analysis in Section 3.2 Final Analyses, responses will be evaluated based on HBsAg level within corresponding efficacy visit windows:

- Primary analysis: (baseline, day 85 + 4 (day89)]
- 3m FU analysis: (baseline, day 169 + 51 (day 220)]
- 6m FU analysis: (baseline, day 270 + 45 (day 315)]
- End of Study analysis: anytime post-baseline

If all HBsAg assessments are missing in the above efficacy visit windows, the subject will be imputed as a non-responder for the corresponding analysis window. For categorical HBsAg data (i.e. responder or failure), if a data point is missing and is preceded (-2 week) and followed (+2 week) in time by values that are "< 0.05" then the missing data point is set to "< 0.05"; otherwise the data point was considered a failure (ie, ≥ 0.05).

7.1.2. Population of Interest

The primary efficacy analyses will be based on the ITT population, unless otherwise specified.

7.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.3.1. Statistical Methodology Specification

Endpoint(s)

- Response Rate (RR)

Model Specification

- The primary efficacy objective is only for Part 2 on ITT population.
- Bayesian logistic regression model (BLRM) (Neuenschwander, 2008) will be used for dose-response. 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.
- Response is 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 (i.e., less or equal to $10^{-1.5}$ (or 3.16%) of baseline value) anytime during the study. If subject has no post-baseline assessment of HBsAg levels, subject will be considered a non-responder.
- For dose d and regimen R, the number of subjects with a response (Y_{dr}) in a treatment arm of size n_{dr} is binomial. Therefore $Y_{dr} | n_{dr} \sim \mathbf{Binomial}(\pi_{dr}, n_{dr})$, with RR:

$$\mathbf{logit}(\pi_{dr}) = \alpha + \beta \log\left(\frac{d}{d^*}\right) + \gamma R,$$

  Where π_{dr} is the response rate for active treatment group with dose d (total dose per 4 weeks) and regimen R ($R = 1$ for regimen 'bi-weekly' and $R = 0$ for regimen 'weekly'); d^* = 480 mg 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.
- Weakly informative priors are assumed:
  $\alpha \sim N(0, var = 100)$,
  $\beta \sim N(0, var = 25)$,
  $\gamma \sim N(0, var = 9)$.
- Posterior distribution of response rates of active treatment arms will be generated using BLRM.
- Posterior distribution of response rates of placebo arm will be generated separately from a Beta distribution using highly entropic prior, i.e., Beta (0.1, 0.1), since it is not expected to have any responder in the placebo arm. Placebo injections will be given in different dosing regimens for the purpose of maintaining the blind. However, all placebo subjects across dosing regimens will be combined in 1 group for 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., $\mathbf{P}(\mathbf{RR_{ACT}} > \mathbf{RR_{PBO}}) \geq \mathbf{90\%}$ where $\mathbf{RR_{ACT}}$ is the RR in active group, $\mathbf{RR_{PBO}}$ is the RR in placebo, and P is the posterior probability.

Model Results Presentation

- Number of responders, posterior mean and 95% equal-tail credible interval of the RR will be reported by each treatment arm and placebo. For each treatment arm, the corresponding $\mathbf{P}(\mathbf{RR_{ACT}} > \mathbf{RR_{PBO}})$ will also be reported. All data relating to responses will be listed (including baseline HBsAg levels and minimum post-baseline HBsAg levels).
- Actual values and change from Baseline values of HBeAg level will be summarized by scheduled assessment and for worst case.

Sensitivity and Supportive Analyses

- A supportive analysis will also be performed using pair-wise comparison in Bayesian framework using the same criteria as mentioned above. For pair-wise model, the RR regardless active or placebo, will have the following model:

  $\mathbf{logit}(\pi_{dr}) = \alpha_{dr}$

  where α_{dr} has the following prior: $\alpha_{dr} \sim N(0, var = 100)$,

- Besides BLRM model and pair-wise comparison results under NRI, both models will also be run for observed case for sensitivity analysis.
- To support analysis on RR, HBsAg value, change from baseline and proportion of subjects achieving ≥ 1.5 log decline will be summarized by visit window as shown below:

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Day 8	8	2	11
Day 15	15	12	18
Day 22	22	19	25
Day 29	29	26	32
Day 36	36	33	39
Day 43	43	40	46
Day 50	50	47	53
Day 57	57	54	60
Day 64	64	61	67
Day 71	71	68	74
Day 78	78	75	81
Day 85	85	82	88
Day 92	92	89	95
Day 99	99	96	106
Day 113	113	107	127
Day 141	141	128	155
Day 169	169	156	220
Day 270	270	221	315
Day 360	360	316	405
Day 450	450	406	Last visit day

If there are two or more values within a time window, the record with smallest values for that window will be used.

7.2. Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

Pharmacodynamic data (HBsAg, HBeAg, HBV DNA) will be listed by subject and summarized descriptively by treatment group/HBeAg status in tabular and graphical formats, as appropriate. Analysis of HBV RNA and HBcrAg will be provided in a separate RAP.

Nadir, Time to Nadir, and Change from Baseline to Nadir of HBsAg and HBeAg will be listed summarized by treatment group and HBeAg status as appropriate.

Correlations between HBsAg in HBeAg-positive and HBeAg-negative subjects will be explored graphically.

Correlations between individual PD data for HBsAg and data for ALT will be explored graphically.

Table 3 provides an overview of the planned pharmacodynamic analyses, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 3 Overview of Planned Pharmacodynamic Analyses

[Endpoint / Parameter/ Display Type]	Untransformed													
	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
HBsAg Values				Y	Y [1]		Y				Y	Y [1]		Y
HBeAg Values				Y	Y [1]		Y				Y	Y [1]		Y
HBV DNA Values							Y							
HBsAg Nadir, time to Nadir and change from baseline to Nadir,				Y										
HBeAg Nadir, time to Nadir and change from baseline to Nadir				Y							Y			
Correlations between HBsAg HBeAg-positive and HBeAg-negative subjects					Y									
Correlations between HBsAg, HBV DNA, HBeAg, and ALT data	Y					Y							Y	

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Separate Mean (+ SD) and Median plots will be generated.

7.3. Exploratory Efficacy Analyses

For Part 2, the rate of seroconversion will be analyzed based on ITT population. The seroconversion is defined as presence of HBV surface antibody (HBsAb) (>= 10 IU/L) and HBsAg seroclearance (defined as HBsAg < 0.05 IU/mL),. Number of subject with seroconversion and the 95% confidence interval of the rate will be reported by each treatment arm and placebo.

8. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population for each study part, unless otherwise specified.

8.1. Exposure to Study Treatment

Exposure to study treatment including the compliance of the number of doses administered and duration of exposure will be presented for each treatment group for Part 2. A dose is defined as one planned administration of the study drug (e.g. two injections in the same visit is considered as one dose). Dose administration for Part 2 will also be displayed in separate listings.

The planned number of dose administered is determined by the subjects' arm regimen (i.e. 6 for Bi-weekly, and 12 for weekly across 12-week treatment). If the subject terminated the study early, his planned number of dose administered is calculated by

- If weekly dose regimen: floor [(end of study date – first dose date)/7] + 1
- If Bi-weekly dose regimen: floor [(end of study date – first dose date)/14] + 1

The compliance of the number of doses administered will be summarized by categories: '< 75%', '75 - < 100%' and '100%'.

8.2. Adverse Events Analyses

Adverse events will be coded using MedDRA version 18.1. The AEs will be summarized by frequency and percentage of the subjects in safety population and will be sorted by System Organ Classes (SOC) in descending order for the total group, secondly by Preferred Term (PT) in descending order for the total group. Adverse events will be summarized in various subsets, including treatment-emergent AEs (TEAEs) by maximum causality, by maximum intensity, leading to treatment discontinuation and SAEs.

A TEAE is defined as an AE with start date between the first dose date of the study medication until the follow-up visit. Any AE starting before the first dose date or after the

follow-up visit will not be included in any summary analyses but will be displayed in the listings.

Adverse event severity is classified as mild (grade = 1), moderate (grade = 2), severe (grade = 3), potentially life threatening (grade = 4) or resulting in death (grade = 5). Adverse events starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports an adverse event more than once within that system organ class (SOC)/ preferred term (PT), the AE with the worst case severity will be used in the corresponding severity summaries.

Relationship to study medication, as indicated by the Investigator, is classified as "not related" or "related". Adverse events with a missing relationship to study medication will be regarded as "related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment and maximum grade and will include the number and percentage of subjects. For each study part, incidence of AEs will be tabulated by SOC, PT and maximum grade.

All AEs leading to withdrawal from study will be identified by using the variable pertaining to outcome of the Adverse Events page of the (e)CRF, and listed separately for each study part.

Serious adverse events (SAEs), including deaths, are those events recorded as "Serious" on the Adverse Events page of the (e)CRF, and will be listed separately for each study part.

Listing of various adverse events experienced by individual subjects and relationship between SOC and verbatim text will be provided for each study part.

AEs will be graded by the clinic using the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (National Institute of Allergy and Infectious Diseases) as defined in the following link:

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Appendix 6.

8.3. Vital Signs

Vital signs will be measured after 5 minutes of rest in the semi-supine or supine position. Temperature and respiration rate will be collected as single measurements.

Vital sign data, as well as change from baseline, will be summarized for each parameter by scheduled assessment.

Vital signs (blood pressure, heart rate, temperature, and weight) will also be listed for each subject.

The number and percentage of subjects out of clinical concern range will be also presented in a summary table.

8.4. Injection Site Reactions

Injection site reactions will be reported as adverse events.

8.5. 12-lead electrocardiograms (ECGs)

The following ECG parameters will be reported for each study part (msec): PR, QRS, QT, QTc, QTcF and HR (bpm). All ECGs will be collected after 5 minutes of rest in the semi-supine or supine position. Triplicate 12-lead ECGs will be obtained at the Screening visit and pre-dose on Day 1. Single 12-lead ECGs will be obtained at all other time points. The average of these assessments will be used as the baseline per Section 13.4.3.1. Also the average will be the representative of the subject at all other time points.

Summary tables including actual values and change from Baseline values will be presented for each ECG results by scheduled assessment.

An ECG outlier analysis will be performed showing the proportion of subjects out of clinical concern range. The overall interpretation of the ECG results (Normal; Abnormal; Not Clinically Significant; and Abnormal, Clinically Significant) will also be summarized.

8.6. Laboratory Measurements

Central laboratory results will be included in the reporting of this study for hematology, clinical chemistry, complement factors and urinalysis.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. The statistics will be presented for baseline, as defined in Section 13.4.3.1, and change from baseline to each scheduled assessment. Presentations will use reported units, as provided by the labs. Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within normal range) and high (above upper limit).

The protocol required parameters to be analyzed are as follows:

- Hematology: Platelet count, RBC count (MCV, MCH), Hemoglobin, Hematocrit, Reticulocyte count, and WBC count with differential*: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils.
- Clinical Chemistry: BUN, Creatinine, GFR, Uric acid, Glucose, Potassium, Sodium, Calcium, Phosphorous, Magnesium, AST, ALT, ALP, GGT, CPK, Total and direct bilirubin, Total protein, Albumin, hs-CRP.
- Coagulation: INR, PT, aPTT
- Complement: C3, C4, C5a, Bb

*If WBC total count exist and either WBC differential absolute count or percentage exist for the same visit and date, then the other will be derived as below:

- Differential Count = WBC total count * differential %
- Differential % = differential count/WBC total count

The normal range and normal indicator will be left blank. DAIDS grade will be derived for WBC differential count for both collected record and converted record.
Complement factors will be summarized using change between maximum level observed post-dose (considering all time points) and pre-study drug administration. Percent change relative to pre-study drug administration will be presented.

Clinical laboratory abnormalities will be graded based on the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (National Institute of Allergy and Infectious Diseases) will be applied to hematology, chemistry and urinalysis only. Abnormalities (DAIDS Grade 1 or higher) for individual subjects will be listed.

Separate summary tables for hematology, chemistry laboratory tests and urinalysis tests will be produced.

9. PHARMACOKINETIC ANALYSES (GSK3389404)

9.1. Overview of Planned Pharmacokinetic Analyses

This section documents the planned PK analysis for GSK3389404; PK analysis for the metabolite, ISIS 505358, is detailed in Section 10.1.

The PK analyses will be based on the “Pharmacokinetic” population, defined for main study (rest of world) and JSS subjects. Japanese subjects in the rest of world group of Part 2 will only be assigned to the main study (rest of world) PK population.

GSK3389404 plasma concentration-time data will be listed by subject and summarized descriptively by treatment group, dosage in once, and HBeAg status in tabular and graphical formats.

GSK3389404 PK parameters will be derived from the concentration-time profiles using WinNonlin for Day 1 data for the JSS subjects enrolled in Japan. The derived PK parameters will be listed by subject and summarized by treatment group, dosage in once,and HBeAg status.

Table 4 provides an overview of the planned analyses, with full details being presented in Appendix 10: List of Data Displays.

Table 4 Overview of Planned Pharmacokinetic Analyses for GSK3389404

Endpoints	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma Drug Concentrations				Y	Y [1] [2]	Y [1]	Y							
Derived PK Parameters				Y	Y		Y	Y			Y			

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (+ SD) and Median plots will be generated.

9.2. Drug Concentration Measurements

Refer to Appendix 5: (Derived and Transformed Data).

9.3. Pharmacokinetic Parameters

9.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 5: (Derived and Transformed Data) for the treatment of concentrations below the assay's lower limit of quantification (LLOQ).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin® 6.4 or higher (Pharsight Corporation, a Certara Company, Princeton, NJ), and/or SAS® Version 9.3 or higher. Graphics will be prepared using the same version of SAS®.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 5 will be determined from the plasma concentration-time data, as data permits, for GSK3389404 on Day 1 for subjects enrolled in Japan in the JSS:
- Dose-normalized C_{max} and AUCs will be also calculated and will be summarized by treatment using descriptive statistics

Table 5 Derived Pharmacokinetic Parameters (Part 2 – JSS)

ParameterParameter	Parameter Description
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (ng·h/mL) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity (ng·h/mL) will be calculated by linear up/log down trapezoidal summation as: $AUC = AUC_{(0-t)} + C(t) / \lambda_z$
$AUC_{(0-8)}$	Area under the concentration-time curve in the plasma from time zero to 8 hours post-dose (ng·h/mL), calculated by linear up/log down trapezoidal summation. Actual elapsed time at 8 hours post-dose will be used for the calculation.
$AUC_{(0-24)}$	Area under the concentration-time curve in the plasma from time zero to 24 hours post-dose (ng·h/mL), calculated by linear up/log down trapezoidal summation. Actual elapsed time at 24 hours post-dose will be used for the calculation.
$\%AUC_{ex}$	The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation (%). $\%AUC_{ex}$ will be calculated as: $[AUC_{(0-\infty)} – AUC_{(0-t)}] / AUC_{(0-\infty)} \times 100$
C_{max}	Maximum observed concentration in plasma (ng/mL), determined directly from the concentration-time data.
T_{max}	Time to reach C_{max} (h), determined directly from the concentration-time data.
$T_{½}$	Apparent terminal half-life (h) will be calculated as: $t_{½} = \ln 2 / \lambda_z$
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
T_{lag}	Lag time before observation of quantifiable concentrations in plasma (h), obtained directly from the observed concentration versus time data.
CL/F	Apparent plasma clearance after extravascular dosing (L/h), calculated as administered dose divided by $AUC_{(0-\infty)}$. No dose adjustments are needed for this calculation.
Vz/F	Apparent plasma volume of distribution after extravascular dosing (L), calculated as CL/F divided by λ_z.

NOTES:

- Additional parameters, such as Lambda_z diagnostic parameters, may be included as required.

9.3.2. Statistical Analysis of Pharmacokinetic Parameters

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic Statistical Analyses
Endpoint(s)
• All endpoints will be natural-log transformed prior to the analysis • Dose Proportionality: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} for JSS
Model Specification
• Dose Proportionality will be assessed separately by means of power model: $Y=\alpha \cdot X^{\beta}$ using the least-squares linear regression model: $[\ln(Y) = \alpha + \beta \cdot \ln(X)]$, where Y denotes the PK parameter being analyzed and X denotes dose. ○ PK parameters will be log transformed prior to analysis ○ For single dosing, Day 1 data from JSS may be combined as appropriate ○ If the power model does not show dose proportionality then pairwise analysis of variance (ANOVA) may be used as an exploratory analysis to understand the dose where dose proportionality fails
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Dose Proportionality: The intercept α and the slope β with corresponding 90% CIs will be estimated and presented for each PK parameter

In addition, the PK-dose relationship will be investigated graphically in order to assess dose proportionality of GSK3389404 using $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} by dosage in once. Graphs will show display either raw PK parameter values or dose-normalized values.

10. SECONDARY STATISTICAL ANALYSES

10.1. Overview of Planned Pharmacokinetic Analyses

The PK analyses of ISIS 505358 data will be based on the PK population and will follow that described for GSK3389404 (Section 9).

ISIS 505358 plasma concentration-time data will be listed by subject and summarized descriptively by treatment group, dosage in once, and HBeAg status in tabular and graphical formats.

ISIS 505358 PK parameters for subjects in the JSS enrolled in Japan will be derived from the concentration-time profiles using WinNonlin if data permit. The derived PK parameters will be listed by subject and, if appropriate, will be summarized by treatment

group and HBeAg status. Of note, CL/F and Vz/F will not be calculated for ISIS 505358 (Table 5).
Dose proportionality analysis will be performed on ISIS 505358 PK parameter data, as data permit.

11. EXPLORATORY STATISTICAL ANALYSES

11.1. Overview of Planned PK/PD Analyses

For JSS subjects, correlation between PK parameters ($AUC_{(0-\infty)}$ and C_{max}) (Day 1) and PD parameters (Nadir, Time to Nadir, and Change from Baseline to Nadir) will be explored graphically.

11.2. Overview of Planned PK Analyses by Race

GSK3389404 plasma PK exposure parameters ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}) will be compared between non-Japanese Asian subjects (Part 1), JSS, and healthy Caucasian subjects (FIH study 202007). Box plots paired with individual value scatter plots will be prepared for each PK parameter for the comparison of population.

12. REFERENCES

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13. APPENDICES

13.1. Appendix 1: Schedule of Activities

13.1.1. Protocol Defined Schedule of Events

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

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

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

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

	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

13.2. Appendix 2: Assessment Windows

13.2.1. Definitions of Assessment Windows for Analyses

For different analysis in Section 3.2 Final Analyses, responses will be evaluated based on HBsAg level within corresponding efficacy visit windows:

- Primary analysis: (baseline, day 85 + 4 (day89)]
- 3m FU analysis: (baseline, day 169 + 51 (day 220)]
- 6m FU analysis: (baseline, day 270 + 45 (day 315)]
- End of Study analysis: anytime post-baseline

To support analysis on RR, HBsAg value, change from baseline and proportion of subjects achieving ≥1.5 log decline will be summarized by visit window as shown below:

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Day 8	8	2	11
Day 15	15	12	18
Day 22	22	19	25
Day 29	29	26	32
Day 36	36	33	39
Day 43	43	40	46
Day 50	50	47	53
Day 57	57	54	60
Day 64	64	61	67
Day 71	71	68	74
Day 78	78	75	81
Day 85	85	82	88
Day 92	92	89	95
Day 99	99	96	106
Day 113	113	107	127
Day 141	141	128	155
Day 169	169	156	220
Day 270	270	221	315
Day 360	360	316	405
Day 450	450	406	Last visit day

If there are two or more values within a time window, the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken.

13.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

13.3.1. Study Phases

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

13.3.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before follow up date (450 study day). • Study Treatment Start Date ≤ AE Start Date ≤ (450 study day).].

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
The currently supported versions of SAS software, R, WinBUGS and WinNonLin software will be used.	
Reporting Area	
HARP Server	us1salx00259
HARP Compound	GSK3389404
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0 • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented in SDTM.	
Generation of RTF Files	
• RTF files will be generated.	

13.4.2. Reporting Standards

General
○ The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
○ GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. ○ Numeric data will be reported at the precision collected on the eCRF. ○ The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
○ Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. ○ Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
○ Unscheduled visits will not be included in summary tables and/or figures. ○ All unscheduled visits will be included in listings.

Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
○ Refer to IDSL Statistical Principals 7.01 to 7.13.	
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics	N, n, arithmetic mean, 95% CI of arithmetic mean, standard deviation (SD), %CV, median, minimum, and maximum.
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log-transformed data and between geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) – 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	t_{max}, %AUC_{ex}, t_{lag}, λ_z, λ_z lower, λ_z upper, λ_z no. of points, rsq
Listings	Interval, number of observations included in calculation of λz, regression coefficient and percent AUC extrapolated (%AUC_{ex})

13.4.3. Baseline Definition & Derivations

13.4.3.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the last value/assessment before the first dose of the study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time (e.g., triplicate 12-lead ECGs), the average of these assessments will be used as the baseline.

13.4.3.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 13.4.3.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Time Point
○ Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. ○ If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. ○ Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
○ Calculated as the number of days from randomization date: • Ref Date = Missing → Study Day = Missing • Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date • Ref Data ≥ Randomization Date → Study Day = Ref Date – (Randomization Date) + 1

13.5.2. Study Population

Demographics
Age
○ GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing day will have this imputed as day '15'. ○ Any subject with a missing date and month will have this imputed as '30th June'. ○ Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
○ Calculated as **Weight (kg) / Height (m)^2**

Extent of Exposure
○ Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 ○ Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. ○ The cumulative dose will be based on the formula: Cumulative Dose = Sum of (Number of Days x Total Daily Dose) ○ If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

Laboratory Parameters
○ If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically

Laboratory Parameters
a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. ○ Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 ○ Example 2: 1 Significant Digit = '> x' becomes x + 0.1 ○ Example 3: 0 Significant Digits = '< x' becomes x – 1

13.5.3. Safety

ECG Parameters
RR Interval
○ IF RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcB is machine read & QTcF is not provided, then: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ ○ If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
○ When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. ○ IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as: $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Parameters
○ If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. ○ Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 ○ Example 2: 1 Significant Digit = '> x' becomes x + 0.1 ○ Example 3: 0 Significant Digits = '< x' becomes x – 1

13.5.4. Pharmacokinetic

- 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).
- Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

PK Concentrations and Parameters

- **How to Handle Values below the Quantification Limit**

For the calculation of individual pharmacokinetic profiles

If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For semilogarithmic log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots.

If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).

NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and from the individual subject plots. In some circumstances, there may be a pharmacokinetic rationale for fluctuation resulting in non-measurable concentrations in the middle of the concentration-time profile (e.g., entero-hepatic recycling, erratic absorption from transdermal/inhaled formulations). In these cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) and subsequent valid concentrations may be retained. A reference line indicating LLQ would then be included in plots.

For the calculation of mean or median pharmacokinetic profiles

When estimating the mean or median value for the concentration at a given time point (i.e., descriptive mean or median curve), the following guidelines should be considered: All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or median profiles. Measurable concentrations which follow more than one consecutive mid-profile NQ will be omitted (set to missing).

The mean/median value at a time-point where one or more samples have NQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the LLQ of the assay. For linear plots, zero concentration value(s) will be included in the plot.

- 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).
- Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

For semilogarithmic log-linear plots, zero concentration value(s) will be assigned a missing value. Zero mean or median values will be included in summary tables.

In certain cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) with proper scientific justification(s). A reference line indicating LLQ would then be included in plots.

It should be noted that a high proportion of NQ values may affect the standard deviation (SD); if more than 30% of values are imputed, then SD will not be displayed. Any table of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of subjects with non-missing values) and number imputed (number of subjects with imputed values (i.e., NQ assigned zero concentration). BQL (Below the Quantification Limit) may be displayed in listings by legacy systems instead of NQ; these abbreviations are interchangeable and mean that a sample has been received, analyzed and a concentration below the LLQ of the assay found.

Scientific judgement and prior knowledge should always be used in applying these guidelines.

How to Handle Anomalous Concentration Values

Individual concentrations deemed to be anomalous will be excluded from the pharmacokinetic analysis and median and mean profiles; such anomalous values will be identified (e.g., flagged by an asterisk or an appropriate footnote) in the data listings of the study report. Anomalous values are those that are inconsistent with known or expected pharmacokinetic behaviour of the drug, and are not defined in a statistical outlier sense. Clear justification must be provided in the report for exclusion of any data. Individual plasma concentration-time profiles by actual time and median/mean profiles by treatment (dose) by nominal time will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e., a linear plot) and one plot on the loge-transformed scale (i.e., semilogarithmic log-linear plot). In addition, a plot showing all individual subjects for each treatment (dose) will be produced (both linear and semilogarithmic log-linear).

13.5.5. Pharmacodynamic

- Correlation between PD parameters, including HBV DNA, HBeAg and HBsAg.

PD Values and Parameters

- HBV DNA (as appropriate), HBsAg, HBeAg levels that are below the LLOQ will be imputed as the number of significant digits in the LLOQ will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '< x' becomes x - 0.1

- Correlation between PD parameters, including HBV DNA, HBeAg and HBsAg.
  - Example 3: 0 Significant Digits = '< x' becomes x – 1
- In the scenario of multiple BLQ values, the Time to Nadir will be to the first BLQ value.

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as below: ○ 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 450 visit. An ongoing subject who misses the Day 450 visit will be considered as lost to follow up. • Withdrawn subjects will be replaced in Part 1 but not be replaced in Part 2. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3 Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will

Element	Reporting Detail
	be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

13.6.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o However, if these results in a date prior to Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. o The AE will then be considered to start on-treatment (worst case). o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

13.7.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

13.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

13.8.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints AUC and C_{max}
Analysis	• Mixed effects
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.	

13.8.2. Dose Proportionality

Dose proportionality of GSK3389404 and ISIS 505358following single-dose administration in JSS will be studied using the power model

$$y = \alpha \times (dose)^{\beta}$$

where y denotes the PK parameter being analyzed [$AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}].

Dose proportionality implies that β = 1 and will be assessed by estimating β along with its 90% confidence interval. The exponent, β, in the power model will be estimated by regressing the $\log_e$-transformed PK parameter on $\log_e$-transformed dose.

$$\text{Log}(y)=\log(\alpha) + \beta * \log(dose)$$

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed, with subject as a random effect or a fixed effect power model will be fitted. The mean slope will be estimated from the power model and the corresponding 90% confidence interval calculated. Point estimates and confidence intervals for the slope will be reported to 4 decimal places with no rounding.

An example of SAS code is included here for the power model approach.

```
ODS output solution=stat
Proc Mixed;
      class subject;
      model logPKvar = logdose /cl alpha=0.1 solution ddfm=kr
run;
```

If the power model does not show dose proportionality then pairwise analysis of variance (ANOVA) may be used as an exploratory analysis to understand the dose where dose proportionality fails. PK parameters will be normalized to the reference dose (30 mg) and then log-transformed prior to

the analysis. Dose will be treated as a categorical variable. Point estimates and 90% confidence intervals for AUCs and C_{max} will be reported to 4 decimal places with no rounding.

An example of SAS code is also included here for the ANOVA approach.

```
ODS output solution=stat;
Proc Mixed;
      class subject treatment; /* treatments are different dose groups
      */
      model logdnPKvar = treatment/cl alpha=0.1 solution;;
      lsmeans treatment; /* assuming one ref and three test treatments
      */
      estimate 'test1 vs ref' treatment -1 1 0 0 /cl alpha=0.1;
      estimate 'test2 vs ref' treatment -1 0 1 0 /cl alpha=0.1;
      estimate 'test3 vs ref' treatment -1 0 0 1 /cl alpha=0.1;
run;
```

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
λ_z	Apparent terminal rate constant
$\%AUC_{ex}$	The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
AdaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AUC	Area under the concentration-time
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity
$AUC_{(0-24)}$	Area under the concentration-time curve in the plasma from time zero to 24 hours post-dose
A&R	Analysis and Reporting
C_{24}	Concentration in the plasma at 24 hours after dosing
CDISC	Clinical Data Interchange Standards Consortium
Change from Baseline to Nadir	Minimum observed change from baseline pharmacodynamic value
CI	Confidence Interval
CL/F	Apparent plasma clearance after extravascular
C_{max}	Maximum observed concentration in plasma
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
GUI	Guidance
HbeAg	Hepatitis B e-antigen
HbsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
JSS	Japan Sub-study
LLOQ	Lower limit of quantification

Abbreviation	Description
LLOD	Lower limit of detection
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
Nadir	Minimum observed pharmacodynamic value
NQ	Non-quantifiable
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
$t_{½}$	Apparent terminal half-life
TA	Therapeutic Area
Time to Nadir	Time to reach Nadir
TFL	Tables, Figures & Listings
t_{lag}	Lag time before observation of quantifiable concentrations in plasma
t_{max}	Time to reach C_{max}
Vz/F	Apparent plasma volume of distribution after extravascular
GSK	GlaxoSmithKline

13.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin
SAS

13.10. Appendix 10: List of Data Displays

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays. The all subjects set will start with x.1xx; the corresponding TLFs for JSS only will be x.2xx. For listing, all subjects (combo) will use 1 – 100 range, while JSS will use 201-300 range. For subgroup table, only combo set will be generated. Below TOC only lists the combo set.

Section (All subjects)	**Tables**	**Figures**
Study Population (Part 2)	1.101 to 1.116	N/A
Efficacy (Part 2)	2.101 to 2.116	2.101 to 2.117
Safety (Part 2)	3.101 to 3.125	3.101 to 3.114
Pharmacokinetic (Part 2)	4.201 to 4.306	4.201 to 4.310
Section (All subjects)	**Listings**	
ICH Listings	1 to 30	
Other Listings	1 to 9	
Section (JSS)	**Tables**	**Figures**
Study Population (Part 2)	1.201 to 1.216	N/A
Efficacy (Part 2)	2.201 to 2.216	2.201 to 2.217
Safety (Part 2)	3.201 to 3.225	3.201 to 3.214
Pharmacokinetic (Part 2)	4.201 to 4.306	4.201 to 4.310
Section (JSS)	**Listings**	
ICH Listings	201 to 231	
Other Listings	201 to 213	

13.10.2. Mock Example Shell Referencing

Mock shell will be in a separate document.

13.10.3. Deliverables

Delivery [Priority] [1]	Description
PA [HL]	Primary Analysis headline
PA [1]	Primary Analysis
3m FU [1]	3 month FU
6m FU [1]	6 month FU
EOS [1]	End of Study

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

13.10.4. Table of Contents of Data Display

13.10.4.1. Study Population Tables

Study Population Tables								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
1.101	[ITT]	ES1	Summary of Subject Disposition (Part 2)		x	x	x	x
1.102	[Screened Population]	ES6	Summary of Screening Status and Reasons for Screening Failure (Part 2)		x	x		x
1.103	[Screened Population]	NS1	Summary of Enrolled Subjects by Country and Site ID (Part 2)		x	x		x
1.104	[ITT]	DV1	Summary of Important Protocol Deviations (Part 2)		X	x	x	x
1.105	[ITT]	DM1	Summary of Demographic Characteristics (Part 2)		HL	x		x
1.106	[ITT]	DM1	Summary of Demographic Characteristics by Sub-Group (Part 2)		x	x		x
1.107	[ITT]	DM1	Summary of Baseline Disease Characteristics (Part 2)		HL	x		x
1.108	[ITT]	DM1	Summary of Baseline Disease Characteristics by Subgroup (Part 2)		x	X		x
1.109	[ITT]	DM11	Summary of Age Ranges (Part 2)		x	X		x
1.110	[ITT]	DM5	Summary of Race and Racial Combinations (Part 2)		x	X		x
1.111	[ITT]	MH4	Summary of Past Medical Conditions (Part 2)		x	X		x
1.112	[ITT]	CM1	Summary of Prior Medications (Part 2)		x	X		x
1.113	[ITT]	CM1	Summary of Concomitant Medications (Part 2)		x	X	x	x
1.114	[ITT]	CM1	Summary of Baseline Nucleos(t)ide Use (Part 2)		x	X		x
1.115	[ITT]	MH4	Summary of Current Medical Conditions (Part 2)		x	X		x

Study Population Tables								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
1.116	[ITT]		Summary of Exposure (Part 2)		HL	X		x

13.10.4.2. Efficacy Tables

Efficacy Tables								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
2.101	[ITT]	RE1a	Summary of Response Rate, Missing = Failure (Part 2)		HL	x	x	x
2.102	[ITT]		Summary of Response Rate by Sub-group, Missing = Failure (Part 2)		x	x	x	x
2.103	[ITT]	RE1a	Summary of Response Rate, Observed Case (Part 2)		x	x	x	x
2.104	[ITT]		Summary of Response Rate by Subgroup, Observed Case (Part 2)		x	x	x	x
2.105	[ITT]	RE1a	Summary of HBsAg Outcome, Missing = Failure (Part 2)		x	x	x	x
2.106	[ITT]	LB1	Summary of HBsAg (log10 IU/ml) Change from Baseline by Visit (Part 2)		HL	x	x	x
2.107	[ITT]		Summary of HBsAg (log10 IU/ml) Change from Baseline by Visit and Subgroup (Part 2)		x	x	x	x
2.108	[ITT]	LB1	Summary of HBsAg (log10 IU/ml) by Visit (Part 2)		x	x	x	x
2.109	[ITT]		Summary proportion of Subject Achieving HBsAg >=1.5 log decline (Part 2)		HL	x	x	x

Efficacy Tables								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
2.110	[ITT]		Summary of HBeAg (log10 IU/ml) by Visit (Part 2)		x	x	x	x
2.111	[ITT]		Summary of HBeAg (log10 IU/ml) Change from Baseline by Visit (Part 2)		x	x	x	x
2.112	[ITT]		Summary of Nadir and Time to Nadir for HBsAg, HBeAg		x	x	x	x
2.113	[ITT]		Summary of Change from Baseline to Nadir for HBsAg, HBeAg		x	x	x	x
2.114	[ITT]		Proportion of Subjects with HBsAg <0.05 IU/mL by Visit - Missing = Failure Analysis		HL	x	x	x
2.115	[ITT]	RE1a	Summary of Rate of Seroconversion (Part 2)		x	x	x	x
2.116	[ITT]		Summary of HBsAb (positive/negative) by visit		x	x	x	x

13.10.4.3. Efficacy Figures

Efficacy Figures								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
2.101	[ITT]		Forest Plot of Posterior Mean Response Rate - BLRM (Part 2)		x	x	x	x
2.102	[ITT]		Density Plot of Posterior Distribution of Response Rate by Dose Group and Dosing Regimen - BLRM (Part 2)		x	x	x	x
2.103	[ITT]	RE8a	Waterfall Plot of Percentage Change at Maximum Reduction from Baseline in HBsAg (Part 2)		x	x	x	x
2.104	[ITT]		Forest Plot of Rate of Seroconversion (Part 2)		x	x	x	x

Efficacy Figures								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
2.105	[ITT]		Plot of Mean HBsAg (log10 IU/ml) Change from Baseline (Part 2)		HL	x	x	x
2.106	[ITT]		Plot of Mean HBsAg (log10 IU/ml) Value by Visit (Part 2)		x	x	x	x
2.107	[ITT]		Individual Plot of HBsAg (log10 IU/ml) Change from Baseline by Treatment (Part 2)		x	x	x	x
2.108	[ITT]		Individual Plot of HBsAg (log10 IU/ml) Value by Treatment (Part 2)		x	x	x	x
2.109	[ITT]		Individual Plot of HBsAg (log10 IU/ml) Value Overlay by Treatment (Part 2)		x	x	x	x
2.110	[ITT]		Individual Plot of HBsAg (log10 IU/ml) Value and ALT Profile (Part 2)		x	x	x	x
2.111	[ITT]		Individual HBsAg (log10 IU/ml) Change from Baseline and ALT Profile (Part 2)		HL	x	x	x
2.112	[ITT]		Individual HBeAg (log10 IU/ml) Change from Baseline (Part 2)		x	x	x	x
2.113	[ITT]		Individual HBeAg (log10 IU/ml) Value (Part 2)		x	x	x	x

Efficacy Figures								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
2.114	[ITT]		Individual Plot of HBsAg, HBeAg and HBV DNA (log10 scale) Change from Baseline vs ALT (Part 2)		HL	x	x	x
2.115	[ITT]		Box Plot for HBsAg by HBeAg Status (Part 2)		x	x	x	x
2.116	[ITT]		Box Plot of HBsAg Nadir, Time to Nadir and Change from baseline to Nadir by HBeAg Status (Part 2)		x	x	x	x
2.117	[ITT]		Individual HBsAg (log10 IU/ml) Change from Baseline and ALT Profile – Fix Y Scale (Part 2)	Use one fix scale for HBsAg data on all subjects and use one fix scale for ALT on all subjects	HL	x	x	x

13.10.4.4. Safety Tables

Safety: Tables								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
Adverse Events								
3.101	[Safety]	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade (Part 2)		x	x	x	x
3.102	[Safety]	AE5B	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade (Part 2)		x	x	x	x

Safety: Tables								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
3.103	[Safety]	AE5B	Summary of Non-Serious Adverse Events by System Organ Class and Preferred Term and maximum Grade (Part 2)		x	x	x	x
3.104	[Safety]	AE3	Summary of Adverse Events by Overall Frequency (Part 2)		HL	x	x	x
3.105	[Safety]	AE3	Summary of Grade 2-4 Adverse Events by Overall Frequency (Part 2)		x	x	x	x
3.106	[Safety]	AE3	Summary of Drug-Related Grade 2-4 Adverse Events by Overall Frequency (Part 2)		x	x	x	x
3.107	[Safety]		Overall Summary of Adverse Events and Lab Abnormalities (Part 2)		HL	x	x	x
3.121	[Safety]	AE5B	Summary of SAE by Overall Frequency		HL	x	x	x
3.122	[Safety]	AE5B	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		x	x	x	x
3.123	[Safety]	AE15	Summary of All Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		x	x	x	x

Safety: Tables								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
3.124	[Safety]		Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade and Subgroup (Part 2)		x	x	x	x
3.125	[Safety]		Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade and Subgroup (Part 2)		x	x	x	x
Lab								
3.108	[Safety]	LB1	Summary of Chemistry Changes from Baseline by Visit (Part 2)		x	x	x	x
3.109	[Safety]		Summary of Chemistry Maximum Grade by Category (Part 2)		x	x	x	x
3.110	[Safety]	LB1	Summary of Hematology Changes from Baseline by Visit (Part 2)		x	x		
3.111	[Safety]		Summary of Hematology Maximum Grade by Category (Part 2)		x	x		
3.112	[Safety]	LB1	Summary of Urinalysis Changes from Baseline by Visit (Part 2)		x	x		
3.113	[Safety]	LB2	Summary of Coagulation Lab Data (Part 2)		x	x	x	x
3.114	[Safety]		Summary of Complement Product Levels after Study Drug Dose (Part 2)		x	x	x	x
ECG								
3.115	[Safety]	EG1	Summary of ECG Findings (Part 2)		x	x		
3.116	[Safety]	EG2	Summary of ECG Changes from Baseline by Visit (Part 2)		x	x		

Safety: Tables								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
3.117	[Safety]	CP_EG11	Summary of Maximum Emergent QTc Values by Category (Part 2)		x	x		
3.118	[Safety]	CP_EG12	Summary of Maximum Change from Baseline in QTc Values by Category (Part 2)		x	x		
Vital Signs								
3.119	[Safety]	VS1	Summary of Vital Sign Changes from Baseline by Visit (Part 2)		x	x		
3.120	[Safety]		Summary of Vital Sign Values by Category (Part 2)		x	x		

13.10.4.5. Safety Figures

Safety: Figures								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
Lab								
3.101	[Safety]	LIVER9	Scatter Plot of Maximum vs. Baseline for ALT (Part 2)		x	x	x	x
3.102	[Safety]	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin (Part 2)		x	x	x	x
3.103	[Safety]		Mean Plot of Liver Functions (Part 2)		HL	x	x	x
3.104	[Safety]		Individual Line Plot of Liver Functions (Part 2)		HL	x	x	x
3.105	[Safety]		Mean Plot of Coagulation Tests (Part 2)		x	x	x	x
3.106	[Safety]		Individual Line Plot of Coagulation Tests (Part 2)		x	x	x	x
3.107	[Safety]		Individual Line Plot of Chemistry Lab Tests (Part 2)		x	x	x	x
3.108	[Safety]		Mean Plot of Chemistry Lab Tests (Part 2)		HL	x	x	x
3.109	[Safety]		Individual Line Plot of Chemistry Lab Tests Overlay by Treatment (Part 2)		HL	x	x	x
3.110	[Safety]		Individual Line Plot of Hematology Lab Tests (Part 2)		x	x		
3.111	[Safety]	AE10	On-treatment Adverse Events occur in more than 1 Subject Sorted by Relative Risk (Part 2)		x	x	x	x
3.112	[Safety]		Mean Plot of Chemistry Lab Tests Change from Baseline		HL	x		
3.113	[Safety]		Mean Plot of Hematology Lab Tests Change from Baseline		HL	x		
3.114	[Safety]		Individual Line Plot of Hematology Lab Tests Overlay by Treatment (Part 2)		x	x		

13.10.4.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.101	[PK]	PK01	Summary of GSK3389404 Plasma Pharmacokinetic Concentration-Time Data [ng/mL] by Treatment Group and HBeAg Status (Part 2)		PA / 3m FU
4.102	[PK]	PK01	Summary of ISIS 505358 Plasma Pharmacokinetic Concentration-Time Data [ng/mL] by Treatment Group and HBeAg Status (Part 2)		PA / 3m FU
4.203	[PK]	PK03	Summary of Derived GSK3389404 Plasma Pharmacokinetic Parameters for Day 1by Treatment Group, Dosage in Once and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.204	[PK]	PK03	Summary of Derived ISIS 505358 Plasma Pharmacokinetic Parameters for Day 1 by Treatment Group, Dosage in Once and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.205	[PK]	PK05	Summary of Log-Transformed Derived GSK3389404 Plasma Pharmacokinetic Parameters for Day 1 by Treatment Group, Dosage in Once and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.206	[PK]	PK05	Summary of Log-Transformed Derived ISIS 505358 Plasma Pharmacokinetic Parameters for Day 1 by Treatment Group, Dosage in Once and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.207	[PK]	PK03	Summary of Derived GSK3389404 Plasma Dose-Normalized Pharmacokinetic Parameters for Day 1by Treatment Group, Dosage in Once, and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.208	[PK]	PK03	Summary of Derived ISIS 505358 Plasma Dose-Normalized Pharmacokinetic Parameters for Day 1 by Treatment Group, Dosage in Once, and HBeAg Status (JSS)	JSS subjects enrolled in Japan only	PA
4.209	[PK]	PK_T1	Assessment of Dose Proportionality of GSK3389404 using Power Model Following a Single Dose (JSS)	JSS subjects enrolled in Japan only	PA

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.210	[PK]	PK_T4	Summary of Results of Dose Proportionality Assessment of GSK3389404 using ANOVA Following a Single Dose (JSS)	JSS subjects enrolled in Japan only	PA
4.211	[PK]	PK_T4	Summary of Results of Dose Proportionality Assessment of ISIS 505358 using ANOVA Following a Single Dose (JSS)	JSS subjects enrolled in Japan only	PA

13.10.4.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.101	[PK]	PK17	Mean (+SD) GSK3389404 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status (Part 2) (Linear and Semi-Log)		PA / 3m FU
4.102	[PK]	PK17	Mean (+SD) ISIS 505358 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status (Part 2) (Linear and Semi-Log)		PA / 3m FU
4.103	[PK]	PK18	Median (range) GSK3389404 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status (Part 2) (Linear and Semi-Log)		PA / 3m FU
4.104	[PK]	PK18	Median ISIS 505358 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status (Part 2) (Linear and Semi-Log)		PA / 3m FU
4.105	[PK]	PK16a	Individual GSK3389404 and ISIS 505358 Plasma Concentration-Time Plot (Part 2) (Linear and Semi-Log)		PA / 3m FU
4.206	[PK]	PK17	Mean (+SD) GSK3389404 Plasma Concentration-Time Plot for Day 1 by Treatment Group, Dosage in Once, and HBeAg Status (JSS) (Linear and Semi-Log)	JSS subjects enrolled in Japan only	PA

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.207	[PK]	PK17	Mean (+SD) ISIS 505358 Plasma Concentration-Time Plot for Day 1 by Treatment Group, Dosage in Once, and HBeAg Status (JSS) (Linear and Semi-Log)	JSS subjects enrolled in Japan only	PA
4.208	[PK]	PK18	Median (range) GSK3389404 Plasma Concentration-Time Plot for Day 1 by Treatment Group, Dosage in Once, and HBeAg Status (JSS) (Linear and Semi-Log)	JSS subjects enrolled in Japan only	PA
4.209	[PK]	PK18	Median ISIS 505358 Plasma Concentration-Time Plot for Day 1 by Treatment Group, Dosage in Once, and HBeAg Status (JSS) (Linear and Semi-Log)	JSS subjects enrolled in Japan only	PA
4.210	[PK]	PK16a	Individual GSK3389404 and ISIS 505358 Plasma Concentration-Time Plot for Day 1 (JSS) (Linear and Semi-Log)	JSS subjects enrolled in Japan only	PA
4.211	[PK]		Box Plot of GSK3389404 PK Exposure Parameters versus Dosage in Once for Day 1 (JSS)	JSS subjects enrolled in Japan only	PA

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.212	[PD]		Scatter Plot of Nadir versus AUC(0-inf) for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.213	[PD]		Scatter Plot of Time to Nadir versus AUC(0-inf) for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.214	[PD]		Scatter Plot of Log10 Change from Baseline to Nadir versus AUC(0-inf) for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.215	[PD]		Scatter Plot of Nadir versus Cmax for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.216	[PD]		Scatter Plot of Time to Nadir versus Cmax for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.217	[PD]		Scatter Plot of Log10 Change from Baseline to Nadir versus Cmax for GSK3389404	JSS subjects enrolled in Japan only	PA/3m FU
4.218	[PK]		Box Plot of GSK3389404 PK Exposure Parameter Comparison by Population for Day 1 (JSS)		PA

13.10.4.8. ICH Listings

ICH: Listings								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
Study Population								
1	[Screened Population]	ES7	Listing of Reasons for Screen Failure (Part 2)		x			x
2	[ITT]	ES2	Listing of Reasons for Study Withdrawal (Part 2)		x	x	x	x

ICH: Listings								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
3	[ITT]	BL1	Listing of Subjects for whom Treatment Blind was Broken During the Study (Part 2)		x	x		x
4	[ITT]	TA1	Listing of Randomized and Actual Treatments (Part 2)		x	x	x	x
5	[ITT]	DV2	Listing of Protocol Deviations (Part 2)		x	x	x	x
6	[ITT]	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations (Part 2)		x	x	x	x
7	[ITT]	SP3	Listing of Subjects Excluded from Any Population (Part 2)		x			x
8	[ITT]	DM2	Listing of Demographic Characteristics (Part 2)		x			x
9	[ITT]	DM9	Listing of Race (Part 2)		x			x
10	[ITT]	CM2	Listing of Prior and Concomitant Medications (Part 2)		x	x	x	x
11	[ITT]	CM2	Listing of Baseline Nucleos(t)ide Use (Part 2)		x			x
12	[ITT]	MH2	Listing of Medical Conditions (Part 2)		x			x
Exposure								
13	[Safety]	EX3	Listing of Exposure Data (Part 2)		x	x	x	x
Adverse Events								
14	[Safety]	AE8	Listing of All Adverse Events (Part 2)		HL	x	x	x
15	[Safety]	AE7	Listing of Subject Numbers for Specified Adverse Events (Part 2)		x	x	x	x
16	[Safety]	AE2	Listing of Relationship between System Organ Class and Verbatim Text (Part 2)		x	x	x	x

ICH: Listings								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
17	[Safety]	AE8	Listing of Non-Fatal Serious Adverse Events (Part 2)		x	x	x	x
18	[Safety]	AE8	Listing of Fatal Serious Adverse Events (Part 2)		x	x	x	x
19	[Safety]	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study (Part 2)		x	x	x	x
30	[Safety]	AE14	Listing of Reasons for Considering as a Serious Adverse Event		x	x	x	x
Lab								
20	[Safety]	LB5	Listing of All Laboratory Data (Part 2)		x	x	x	x
21	[Safety]	LB5	Listing of All Laboratory Data for Subjects with any Grade 1 or Higher Abnormality (Part 2)		x	x	x	x
22	[Safety]	LB5	Listing of All Laboratory Data with Grade 1 or Higher (Part 2)		x	x	x	x
ECG								
23	[Safety]	CP_EG3	Listing of All ECG Data (Part 2)		x	x		

ICH: Listings								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
24	[Safety]	CP_EG3	Listing of All ECG Data for Subjects with Any Value of Potential Clinical Importance (Part 2)		x	x		
25	[Safety]		Listing of All ECG Findings (Part 2)		x	x		
26	[Safety]	CP_EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding (Part 2)		x	x		
Vital Signs								
27	[Safety]	CP_VS4	Listing of All Vital Signs (Part 2)		x	x		
28	[Safety]	CP_VS4	Listing of All Vital Signs for Subjects with Any Values of Potential Clinical Importance (Part 2)		x	x		
Liver								
29	[Safety]	LIVER5	Listing of Liver Stopping/Monitoring Event Reporting (Part 2)		x	x	x	x

13.10.4.9. Non-ICH Listings

Non-ICH: Listings								
No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable			
					PA	3mFU	6mFU	EOS
Efficacy								
1	[ITT]	RE5a	Listing of Response based on HBsAg (Part 2)		x	x	x	x
2	[ITT]	RE5a	Listing of HBsAb and Seroconversion (Part 2)		x	x	x	x
3	[ITT]		Listing of HBsAg and HBeAg		x	x	x	x

Non-ICH: Listings								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
4	[ITT]		Listing of HBV DNA Value for subject with Virologic Breakthrough		HL	x	x	x
5	[ITT]		Listing of HBV DNA Value		x	x	x	x
PK								
106	[PK]	PK08	Listing of GSK3389404 Plasma Pharmacokinetic Concentration-Time Data by Treatment Group and Study Day (Part 2)		PA / 3m FU			
107	[PK]	PK08	Listing of ISIS 505358 Plasma Pharmacokinetic Concentration-Time Data by Treatment Group and Study Day (Part 2)		PA / 3m FU			
108	[PK]	Non-Standard PK L_1	Individual GSK3389404 Plasma Concentrations (ng/mL) by Scheduled Time (Part 2)		PA / 3m FU			
109	[PK]	Non-Standard PK L_1	Individual ISIS 505358 Plasma Concentrations (ng/mL) by Scheduled Time (Part 2)		PA / 3m FU			
210	[PK]	PK14	Listing of Derived GSK3389404 Plasma Pharmacokinetic Parameters for Day 1 for Each Treatment Group (JSS)	JSS subjects enrolled in Japan only	PA			
211	[PK]	PK14	Listing of Derived ISIS 505358 Plasma Pharmacokinetic Parameters for Day 1 for Each Treatment Group (JSS)	JSS subjects enrolled in Japan only	PA			

Non-ICH: Listings								
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**			
					PA	**3mFU**	**6mFU**	**EOS**
212	[PK]	PK14	Individual GSK3389404 Plasma Lambda_z Related Pharmacokinetic Parameters for Each Treatment Group (JSS)	JSS subjects enrolled in Japan only	PA			
213	[PK]	PK14	Individual ISIS 505358 Plasma Lambda_z Related Pharmacokinetic Parameters for Each Treatment Group (JSS)	JSS subjects enrolled in Japan only	PA			

13.11. Appendix 11: Bayesian Modelling Details

13.11.1. PROC MCMC Parameters Settings and Validation

Parameters	Value
Seeds	1
Number of chains	2
Blocking of parameters	All-at-once; e.g. parm alpha beta gamma;
Order of priors	Alpha beta gamma
Number of burn-in	5000
Number of MCMC after burn-in	100000

Initials for chains:

- For BLRM

Chain	Alpha	Beta	gamma
1	0	0	0
2	-1	1	1

- For Placebo with beta prior

Chain	p
1	0.5
2	0.1

- For placebo with logistic model with single intercept

Chain	Alpha
1	0
2	1

- For pair-wise comparison

Chain	Alpha0	Alpha30	Alpha60	Alpha120bw	Alpha120w
1	0	0	0	0	0
2	1	-1	1	-1	1

Due to the nature of MCMC, for validation purpose, criterion will be set to be dependent on the total SD. For example, the estimated MCMC error, for each chain, should be < 5% of its associated SD.

13.11.2. MCMC Mixing Diagnosis

Two sampling chains will be run, with differing starting values and each with a burn-in period of 5,000 samples, to ensure adequate sampling from the posterior. The starting values will be as above section.

Mixing will be regarded as “each chain is independently realizing values similar to those for which the other chains have also sampled.” Adequate mixing will be concluded if the chains meet all of the following conditions, in conjunction with the following actions:

1. The Brooks-Gelman Ratio (BGR) (Brooks, 1998) for each parameter is in the interval (0.8, 1.2).
2. Each chain will begin with length 100000. The chain will be doubled in length until the estimated MCMC error, for each chain, is less than 5% of its associated SD.
3. If computer memory limitations impede increasing the length of a chain enough to meet the MCMC error criterion above, then thinning will be used to reduce the autocorrelation of the chain. The maximum thinning value acceptable will be 100. The thinning values will be the prime numbers less than 100 starting at two. In the end, the chains will be thinned by the smallest prime number less than 100 for which the autocorrelations are less than 0.10 by 10 iterations. If no such prime value is found then the model will be reparameterized using algebraically equivalent formulations and then rerun.
4. Each chain appears mix well, upon visual inspection of each chain’s trace plot, including assessing the mutual overlap of the chains for each parameter.
5. Each kernel density plot appears smooth upon visual inspection.

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 205670: 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 (Part 1)
Compound Number	:	GSK3389404
Effective Date	:	28-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205670: 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.
- The RAP was developed in 2016 - 2017 based on 2014 RAP template with a final draft in September 2017. The 2014 RAP template used for the RAP was the latest version at the time of RAP development.

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PPD Director, Clinical Statistics, GSK	05-JUN-2018
PPD Manager, Clinical Programming, GSK	28-JUN-2018

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This reporting and analysis plan (RAP) details planned analyses for a clinical study report for study 205670 which will be used to support the regulatory submissions for the treatment of subjects with chronic Hepatitis B (CHB).
Protocol	• This RAP is based on the protocol amendment number 3 [(Dated: 28JUN2017) of study 205670 (GSK Document No.: 2016N277028_04)].
Primary Objectives	• To assess the safety, tolerability, and PK profile of GSK3389404 in single (Part 1) administration in subjects with CHB.

Primary Endpoints	• Safety and Tolerability
	  • As measured by clinical assessments including, but not limited to
	  • Vital signs
	  • Physical examinations
	  • 12-lead electrocardiograms (ECGs)
	  • Laboratory measurements (hematology, clinical chemistry, coagulation parameters, complement and urinalysis)
	  • Adverse events (AEs), serious adverse events (SAEs), discontinuations
	• 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).

Secondary Endpoints	• Pharmacodynamic:
	  • 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).
	• Pharmacokinetic:
	  • Derived ISIS 505358 plasma PK parameters including, but not limited to area under the concentration-time curve (AUC), maximum observed concentration (Cmax), time of maximum observed concentration (tmax), and terminal half-life (t½).

Study Design	• Part 1 will be conducted as a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study with 5 planned cohorts. • Cohort A (HBeAg-positive and/or HBeAg –negative subjects):

Overview	Key Elements of the RAP
	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. The decision to enrol the optional Cohort C1 will be made at a prior Dose Escalation Committee Meeting. Dose Escalation Committee meetings will be held between sequential cohorts. • 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.
Planned Analyses	• No formal interim analysis is planned for Part 1. • A preliminary PK analysis will be performed after each dose level is completed and the Dose Escalation Committee 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. • The final analysis and reporting of Part 1 may be conducted prior to the completion of Part 2.
Analysis Populations	• All Subjects Screened Population • Safety Population • Pharmacokinetic Population • Pharmacodynamic Population • Intent-to-Treat (ITT) Population
Hypothesis	• No formal hypotheses are to be tested in Part 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. • Pharmacokinetics (GSK3389404)

Overview	Key Elements of the RAP
	• 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 $AUC_{(0-8)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, 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.

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)
	  • 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 $AUC_{(0-8)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, 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.

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.

2. SUMMARY OF KEY PROTOCOL INFORMATION

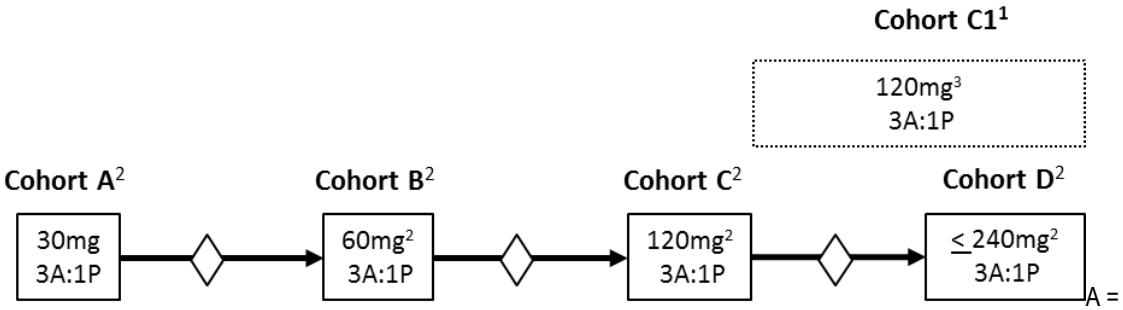
2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the planned statistical analysis specified in the protocol [(Dated: 28JUN2017)].

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety, tolerability, and PK profile of GSK3389404 in single (Part 1) in subjects with CHB.	• Safety and Tolerability As measured by clinical assessments including, but not limited to o Vital signs o Physical examinations o 12-lead electrocardiograms (ECGs) o Laboratory measurements (e.g., chemistry, hematology) o 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).
Secondary Objectives	**Secondary Endpoints**
• To assess the PD effect of GSK3389404 in subjects with CHB (Part 1).	• Correlation between GSK3389404 PK parameters and PD parameters, including HBV 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, following single and multiple dose administration of GSK3389404 (Part 1).	• Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.
Exploratory Objectives	**Exploratory Endpoints**
• To assess PD differences in HBeAg-positive and HBeAg-negative subjects with CHB (Part 1, if applicable).	• Correlation between PD parameters, including HBV DNA, HBV RNA, HBsAg, and/or hepatitis B core related antigen (HBcrAg).

2.3. Study Design

Overview of Study Design and Key Features
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 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. • Dose escalation can only occur after the Dose Escalation Committee 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. **Figure 1 Part 1: Single Ascending Dose, Study Design Schematic**    A = active (GSK3389404); HBeAg = hepatitis B virus e-antigen; P = placebo. ◊ = Dose Escalation Committee 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.

Dosing	Part 1, SAD: • Cohort A: GSK3389404 30 mg SC or placebo • Cohort B: GSK3389404 60 mg SC or placebo • Cohort C: GSK3389404 120 mg SC or placebo • Cohort C1 (HBeAg-positive or HBeAg-negative subjects): GSK3389404 120 mg SC or placebo

Overview of Study Design and Key Features	
	• Cohort D: GSK3389404 <= 240 mg SC or placebo
Treatment Assignment	Separate randomization schedules will be generated for each part of the study (Part 1). Part 1: • Subjects 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]). • Subjects that withdraw from Part 1 of the study may be replaced. The new subject will be assigned to receive the same study treatment as the subject being replaced.
Interim Analysis	• No formal interim analysis is planned for Part 1.
Rules for Safety Concern	Part 1: • 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. • Dose escalation can only occur after the Dose Escalation Committee has 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). • Additional dose(s) may also be considered to further assess safety, tolerability, PK, and/or PD.
Type and Number of Subjects	• Adult male and female subjects with CHB between18 and 70 years of age, inclusive, and not currently receiving CHB treatment are planned for inclusion. • Part 1 (Cohorts A, B, C and D) will enroll HBeAg-positive and/or HBeAg-negative subjects. • Part 1 (optional Cohort C1) may enroll HBeAg-positive or HBeAg-negative subjects (or none at all). 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.

2.4. Statistical Hypotheses

No formal hypotheses are to be tested in Part 1.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analysis is planned for Part 1.

For Part 1, however, a preliminary PK analysis will be performed after each dose level is completed and the Dose Escalation Committee 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.

3.2. Final Analyses

The final planned analysis for Part 1 will be performed after the completion of the following sequential steps:

1. All subjects have completed the study or been considered as lost to follow-up.
    - 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.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared for Part 1 by Data Management.
3. All criteria for unblinding the randomization codes have been met.

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Screened	• The All Subjects Screened Population will include all subjects who consent to participate in the clinical trial. • The population will be defined separately for Part 1 and Part 2.	• Screen failure summary.
Safety	• Include all subjects who receive at least one dose of the study treatment (including placebo) • This population will be based on the treatment the subject actually received. • The population will be defined separately for Part 1 and Part 2.	• Safety
Intent-To-Treat (ITT)	• Comprise of all randomized subjects. • This population will be based on the	• Efficacy • Study Population

Population	Definition / Criteria	Analyses Evaluated
	treatment to which the subject was randomized. • Any subject who receives a treatment randomization number will be considered to have been randomized.	
Pharmacokinetic (PK)	• Include all subjects in the Safety population for whom at least one evaluable PK sample will be obtained and analyzed. • PK samples that may be affected by protocol deviations will be reviewed by the study team and determined whether or not the sample will be excluded. • The population will be defined separately for Part 1 and Part 2 of the study.	• PK
Pharmacodynamic (PD)	• Include all subjects in the Safety population who provide evaluable PD data.	• PD

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.1	Appendix 1: Treatment Phases
Section 11.2	Appendix 2: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.3	Appendix 3: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic
Section 11.4	Appendix 4: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.5	Appendix 5: Values of Potential Clinical Importance
Section 11.6	Appendix 6: Model Checking and Diagnostics for Statistical Analysis
Section 11.7	Appendix 7: Pharmacokinetic Analysis
Other RAP Appendices	
Section 11.8	Appendix 8: Abbreviations & Trade Marks
Section 11.9	Appendix 9: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Randomization			
Randomization			Y
Subject Disposition			
Number of Subjects Enrolled by Country and Site	Y		
Subject Disposition	Y		
Screen Failures	Y		Y
Reason for Withdrawals			Y
Important Protocol Deviations	Y		Y
Demography			
Demographics	Y		Y
Baseline Disease Characteristics	Y		Y
Race & Racial Combinations	Y		Y
Age Ranges	Y		
Subjects Excluded from Study Populations			Y
Medical Condition & Concomitant Medications			
Past/Current Medical Conditions	Y		Y
Concomitant Medications	Y		Y
Baseline Nucleos(t)ide Use	Y		Y

NOTES :

- Y = Yes display generated.

6.1.1. Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study. In each study part, subject disposition will be tabulated for each study treatment and for all subjects combined with the number of subjects who complete the study, prematurely discontinue, and the reason (primary and secondary, if available) for early discontinuation. Summaries will also be provided for number of subjects enrolled by site, reasons for screen failure and important protocol deviations.

Listings of inclusion/exclusion criteria deviations, reasons for screen failure, early withdrawal, treatment randomization, important protocol deviations and study treatment administration will be provided for each study part.

6.1.2. Demographic and Baseline Characteristics

Individual subject demographics, race and racial combinations, age ranges and subjects excluded from study populations will be presented in listings for each study part.

Demographic characteristics such as age, sex, race, ethnicity, child bearing potential, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment and for all subjects overall for each study part. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percent will be presented for age category, sex, race, ethnicity and child bearing potential.

Other baseline characteristics include but not limited to drug/alcohol use, HIV, HDV and hepatitis C information at screening, quantitative HBsAg and quantitative HBV DNA, HBeAg status [±], HBeAg level, ALT level [x ULN] and HBV viral genotype.

6.1.3. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed for each study part using generic term, verbatim text, and indication. The summary of prior and concomitant medications will show the number and percentage of subjects taking prior and concomitant medications and corresponding Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information.

Please refer to Appendix 1 for definition of prior, concomitant and post-treatment medications. Handling of partial dates for medications is outlined in Appendix 4: Premature Withdrawals & Handling of Missing Data.

6.1.4. Medical History and Current Medical Conditions

Medical history and current medical conditions will be summarized and display the number and percentage of subjects for each body system.

6.1.5. Treatment Exposure

Summary includes duration of treatment, the number of doses administered and total volumes of doses. Dose administration for all subjects in Part 1 will be displayed in the listing.

7. PRIMARY STATISTICAL ANALYSES

The efficacy analyses will be conducted only for Part 2. Other analyses will be applied to both Part 1 and Part 2.

7.1. Efficacy Analyses

The efficacy analyses will be conducted only for Part 2.

7.2. Safety Analyses

7.2.1. Overview of Planned Safety Analysis

The primary safety analyses will be based on the "Safety" population for each study part, unless otherwise specified.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by cohort, subject and time; summaries will be presented by treatment and time. In general, tables, figures and listings will be presented separately for Part 1 and Part 2. Subjects receiving placebo will be combined into one treatment group in the summaries within each part.

For categorical variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of variable will be presented. Continuous variables will be summarized using descriptive statistics, including N, mean, standard deviation (SD), median, minimum and maximum values. Geometric mean will be included for PK parameters, where applicable.

Table 3 provides an overview of the planned safety analyses for each study part, unless otherwise specified, with full details of data displays being presented in Appendix 9: List of Data Displays

Table 3 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Exposure	Y			Y				
Adverse Events								
All AE's	Y			Y				
All Drug-Related AEs	Y							
Serious AEs	Y			Y				
AEs Leading to Withdrawal/Permanent Discontinuation of Study Treatment	Y			Y				
Laboratory Values								
DAIDS Grading	Y			Y				
Hematology					Y			

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Chemistry			Y		Y			
Urinalysis					Y			
Complement Factors					Y			
Serum Creatinine, Creatinine Phosphokinase, Platelet			Y					
ECG's								
Potential Clinical Importance				Y				
ECG Findings	Y			Y				
ECG Values					Y			
Vital Signs								
Potential Clinical Importance				Y				
Vitals Values					Y			
Other								
Injection Site Reactions				Y				
Study Treatment Discontinuation				Y				

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.2.2. Exposure to Study Treatment

Dose administration for Part 1 will also be displayed in separate listings.

7.2.3. Adverse Events

Adverse events will be coded using MedDRA version 18.1. The AEs will be summarized by frequency and percentage of the subjects in safety population and will be sorted by System Organ Classes (SOC) in descending order for the total group, secondly by Preferred Term (PT) in descending order for the total group. Adverse events will be summarized in various subsets, including treatment-emergent AEs (TEAEs) by maximum causality, by maximum intensity, leading to treatment discontinuation and SAEs.

A TEAE is defined as an AE with start date between the first dose date of the study medication until the follow-up visit. Any AE starting before the first dose date or after the follow-up visit will not be included in any summary analyses but will be displayed in the listings.

Adverse event severity is classified as mild (grade = 1), moderate (grade = 2), severe (grade = 3), potentially life threatening (grade = 4) or resulting in death (grade = 5). Adverse events starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports an adverse event more than once within

that system organ class (SOC)/ preferred term (PT), the AE with the worst case severity will be used in the corresponding severity summaries.

Relationship to study medication, as indicated by the Investigator, is classified as "not related" or "related". Adverse events with a missing relationship to study medication will be regarded as "related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment and maximum grade and will include the number and percentage of subjects. For each study part, incidence of AEs will be tabulated by SOC, PT and maximum grade.

All AEs leading to withdrawal from study will be identified by using the variable pertaining to outcome of the Adverse Events page of the (e)CRF, and listed separately for each study part.

Serious adverse events (SAEs), including deaths, are those events recorded as "Serious" on the Adverse Events page of the (e)CRF, and will be listed separately for each study part.

Listing of various adverse events experienced by individual subjects and relationship between SOC and verbatim text will be provided for each study part.

AEs will be graded by the clinic using the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (National Institute of Allergy and Infectious Diseases) as defined in the following link:

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Section 11.4.2.

7.2.4. Vital Signs

Vital signs will be measured after 5 minutes of rest in the semi-supine or supine position. Temperature and respiration rate will be collected as single measurements.

Vital sign data, as well as change from baseline, will be summarized for each parameter by scheduled assessment.

Vital signs (blood pressure, heart rate, temperature, and weight) will also be listed for each subject.

The number and percentage of subjects with clinically relevant abnormalities will be also presented in a summary table.

7.2.5. Physical Examinations

Physical examination results will be listed only.

Clinically significant abnormalities observed in physical examination results occurring after administration of study drug will be recorded as adverse events.

7.2.6. Injection Site Reactions

Injection site reactions will be reported as adverse events.

7.2.7. 12-lead electrocardiograms (ECGs)

The following ECG parameters will be reported for each study part (msec): PR, QRS, QT, QTc, QTcF and HR (bpm). All ECGs will be collected after 5 minutes of rest in the semi-supine or supine position. Triplicate 12-lead ECGs will be obtained at the Screening visit and pre-dose on Day 1. Single 12-lead ECGs will be obtained at all other time points. The average of these assessments will be used as the baseline per Section 11.2.2.1. Also the average will be the representative of the subject at all other time points.

Summary tables including actual values and change from Baseline values will be presented for each ECG results by scheduled assessment.

An ECG outlier analysis will be performed showing the proportion of subjects out of clinical concern range. The overall interpretation of the ECG results (Normal; Abnormal; Not Clinically Significant; and Abnormal, Clinically Significant) will also be summarized.

7.2.8. Laboratory Measurements

Central laboratory results will be included in the reporting of this study for hematology, clinical chemistry, complement factors and urinalysis.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. The statistics will be presented for baseline, as defined in Section 11.2.2.1, and change from baseline to each scheduled assessment. Presentations will use reported units, as provided by the labs. Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within normal range) and high (above upper limit).

The protocol required parameters to be analyzed are as follows:

- Hematology: Platelet count, RBC count (MCV, MCH), Hemoglobin, Hematocrit, Reticulocyte count, and WBC count with differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils.
- Clinical Chemistry: BUN, Creatinine, GFR, Uric acid, Glucose, Potassium, Sodium, Calcium, Phosphorous, Magnesium, AST, ALT, ALP, GGT, CPK, Total and direct bilirubin, Total protein, Albumin, hs-CRP.
- Coagulation: INR, PT, aPTT.

- Complement: C3, C4, C5a, Bb

Summaries of subject shifts in grade will be provided. These summaries will display the number and percentage of subjects with a maximum grade during each assessment time based on their baseline grade.

Complement factors will be summarized using change between maximum level observed post-dose (considering all time points) and pre-study drug administration. Percent change relative to pre-study drug administration will be presented.

Clinical laboratory abnormalities will be graded based on the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (National Institute of Allergy and Infectious Diseases) will be applied to hematology, chemistry and urinalysis only. Abnormalities (DAIDS Grade 1 or higher) for individual subjects will be listed.

Separate summary tables for hematology, chemistry laboratory tests and urinalysis tests will be produced.

7.2.9. Study Treatment Discontinuation

For each study part, a listing will present subjects for whom the study treatment was stopped together with the reason and the status of subject.

7.3. Pharmacokinetic Analyses (GSK3389404)

7.3.1. Overview of Planned Pharmacokinetic Analyses

The PK analyses will be based on the "Pharmacokinetic" population.

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 will be listed by subject and summarized by treatment group and HBeAg status.

Table 4 provides an overview of the planned analyses, with full details being presented in Appendix 9: List of Data Displays.

Table 4 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma Drug Concentrations				Y	Y [1] [2]	Y [1]	Y							
Derived PK Parameters				Y			Y	Y			Y			

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (+ SD) and Median plots will be generated.

7.3.2. Drug Concentration Measurements

Refer to Appendix 2: Data Display Standards & Handling Conventions (Reporting Process & Standards).

7.3.3. Pharmacokinetic Parameters

7.3.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 2: Data Display Standards & Handling Conventions (Reporting Process & Standards) for the treatment of concentrations below the assay's lower limit of quantification (LLQ).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin® (WNL) 6.4 or higher (Pharsight Corporation, a Certara Company, Princeton, NJ), and/or SAS® Version 9.3 or higher. Graphics will be prepared using the same version of SAS®.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- In WNL, when the terminal slope cannot be estimated using the default fit method of "BestFit", consult GSK ClinPharm rep (Kelong Han). GSK ClinPharm rep will determine whether to exclude this subject / profile due to atypical PK profile, or will select the fit method of "TimeRange" with specific time points.
- Pharmacokinetic parameters described in Table 5 will be determined from the plasma concentration-time data, as data permits, for GSK3389404 on Day 1 of Part 1:

Table 5 Derived Pharmacokinetic Parameters (Part 1)

Parameter	Parameter Description
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (ng·h/mL), calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-8)}$	Area under the concentration-time curve from time zero to 8 hours post-dose (ng·h/mL), calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Actual elapsed time at 8 hours post-dose will be used for the calculation.
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity (ng·h/mL), calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for

Parameter	Parameter Description
	each decremental trapezoid (AUCINF_pred in WNL) as: $AUC = AUC_{(0-t)} + C(t) / \lambda_z$ where C(t) is the predicted concentration at the final observation time.
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post-dose (ng·h/mL), calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Actual elapsed time at 24 hours post-dose will be used for the calculation.
$\%AUC_{ex}$	The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation (%). $\%AUC_{ex}$ will be calculated as: $[AUC_{(0-\infty)} – AUC_{(0-t)}] / AUC_{(0-\infty)} \times 100$
C_{max}	Maximum observed concentration in plasma (ng/mL), determined directly from the concentration-time data.
t_{max}	Time to reach C_{max} (h), determined directly from the concentration-time data.
C_{24}	Concentration in the plasma at 24 hours after dosing (ng/mL), obtained from interpolation of the observed concentration versus time data.
$t_{½}$	Apparent terminal half-life (h) will be calculated as: $t_{½} = \ln 2 / \lambda_z$
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
t_{lag}	Lag time before observation of quantifiable concentrations in plasma (h), obtained directly from the observed concentration versus time data.
CL/F	Apparent subcutaneous plasma clearance after extravascular dosing (L/h), calculated as administered dose divided by AUC(0-∞). No dose adjustments are needed for this calculation.

NOTES:

- Additional parameters may be included as required.

7.3.3.2. Statistical Analysis of Pharmacokinetic Parameters

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic Statistical Analyses
Endpoint(s)
• All endpoints will be natural-log transformed prior to the analysis • Dose Proportionality: $AUC_{(0-t)}$, $AUC_{(0-8)}$, $AUC_{(0-\infty)}$, and C_{max} for Part 1
Model Specification
• Dose Proportionality in Part 1 will be assessed separately by means of power model: $Y=\alpha \cdot X^{\beta}$ using the least-squares linear regression model: $[\ln(Y) = \alpha + \beta \cdot \ln(X)]$, where Y denotes the PK parameter being analyzed and X denotes dose. o PK parameters will be log transformed prior to analysis o For single dosing, Day 1 data from Part 1 may be combined as appropriate

Pharmacokinetic Statistical Analyses
○ If the power mode does not show dose proportionality then pairwise analysis of variance (ANOVA) may be used as an exploratory analysis to understand the dose where dose proportionality fails
Model Checking & Diagnostics
• Refer to Appendix 6: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Dose Proportionality: The intercept α and the slope β with corresponding 90% CIs will be estimated and presented for each PK parameter

8. SECONDARY STATISTICAL ANALYSES

8.1. Pharmacodynamic Analyses

8.1.1. Overview of Planned Pharmacodynamic Analyses

The pharmacodynamic analyses will be based on the "Pharmacodynamic" population.

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

PD parameters (Nadir, Time to Nadir, and Log10 Change from Baseline to Nadir) will be derived from the concentration-time profiles using WinNonlin or SAS. The derived PD parameters will be listed by subject and summarized by treatment group and HBeAg status.

Correlations between PD data in HBeAg-positive and HBeAg-negative subjects will be explored graphically. Correlation between PK parameters ($AUC_{(0-\infty)}$ and C_{max}) and PD parameters (Nadir, Time to Nadir, and Log10 Change from Baseline to Nadir) will also be explored graphically.

Correlations between individual PD data for HbsAg and data for ALT will be explored graphically.

Table 6 provides an overview of the planned pharmacodynamic analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 6 Overview of Planned Pharmacodynamic Analyses

[Endpoint / Parameter/ Display Type]	Untransformed													
	Absolute							Log10 Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
HBsAg Values				Y	Y [1]		Y				Y	Y [1]		Y
HBeAg Values				Y	Y [1]		Y				Y	Y [1]		Y
HBV DNA Values				Y	Y [1]		Y				Y	Y [1]		Y
HBV RNA Values				Y	Y [1]		Y				Y	Y [1]		Y
HbcrAg Values				Y	Y [1]		Y				Y	Y [1]		Y
HBsAg Parameters				Y							Y			
HBeAg Parameters				Y							Y			
HBV DNA Parameters				Y							Y			
HBV RNA Parameters				Y							Y			
HbcrAg Parameters				Y							Y			
Correlations between PD in HBeAg-positive and HBeAg-negative subjects					Y									
Correlations between PD and PK Parameters						Y							Y	
Correlations between HbsAg, HBV DNA, HbeAg, and ALT data						Y							Y	

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Separate Mean (+ SD) and Median plots will be generated.

8.2. Pharmacokinetic Analyses (ISIS 505358)

8.2.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses of ISIS 505358 data will be based on the PK population and will follow that described for GSK3389404.

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 will be listed by subject and summarized by treatment group and HbeAg status.

The results of dose proportionality analysis of ISIS 505358 data will be presented in tabular format, separately for each Part.

9. EXPLORATORY STATISTICAL ANALYSES

9.1. Pharmacodynamic Analyses

Pharmacodynamic data (HbsAg, HbeAg, HBV DNA, HBV RNA, and HbcrAg) and PD parameters will be listed by subject and summarized separately for HbeAg-positive and HbeAg-negative subjects with CHB in tabular and graphical formats, as appropriate (Part 1, if applicable).

9.2. Rate of Seroconversion

No analysis will be performed for rate of seroconversion for Part 1.

10. REFERENCES

GSK Document Number 2016N277028_04. Study 205670 Protocol Amendment 03 Effective 28 JUN 2017.

Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to Phase I cancer trials. *Statistics in Medicine*, 27:2420-39.

11. APPENDICES

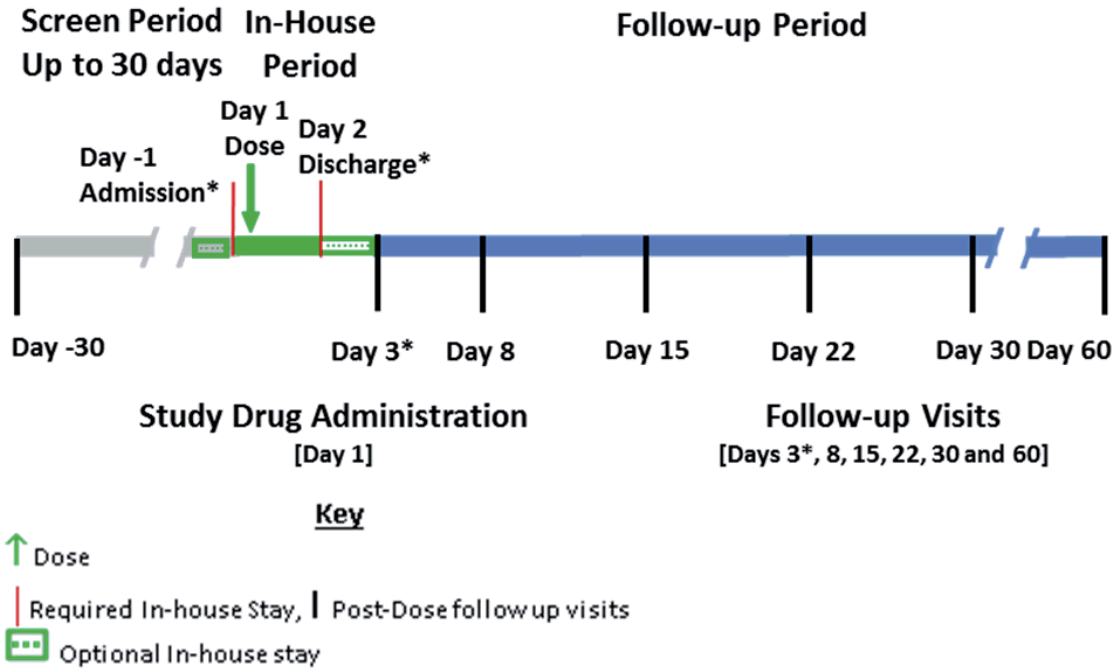
Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.1	Appendix 1: Treatment Phases
Section 11.2	Appendix 2: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.3	Appendix 3: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 11.4	Appendix 4: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.5	Appendix 5: Values of Potential Clinical Importance
Section 11.6	Appendix 6: Model Checking and Diagnostics for Statistical Analysis
Section 11.7	Appendix 7: Pharmacokinetic Analysis
Other RAP Appendices	
Section 11.8	Appendix 8: Abbreviations & Trade Marks
Section 11.9	Appendix 9: List of Data Displays

11.1. Appendix 1: Treatment Phases

11.1.1. Treatment Phases

Part 1 is a SAD study, thus subjects will receive treatment dose on Day 1. 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 2 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.

11.2. Appendix 2: Data Display Standards & Handling Conventions

11.2.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions for Part 1
Data Displays for Reporting
Description
Placebo
GSK3389404 30mg
GSK3389404 120mg
All Active
Total
Placebo (HBeAg-)
GSK3389404 30mg (HBeAg-)
GSK3389404 120mg (HBeAg-)
All Active (HBeAg-)
Total (HBeAg-)
Placebo (HBeAg+)
GSK3389404 30mg (HBeAg+)
GSK3389404 120mg (HBeAg+)
All Active (HBeAg+)
Total (HBeAg+)

11.2.2. Baseline Definition & Derivations

11.2.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the last value/assessment before the first dose of the study treatment (Day 1 pre-dose). If there are multiple assessments collected at the same scheduled time (e.g., triplicate 12-lead ECGs), the average of these assessments will be used as the baseline.

11.2.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Log10 Change from Baseline	log10(Post-Dose Visit Value / Baseline)
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change
Maximum Log10 Change from Baseline	= Calculate the log10 change from baseline at each given timepoint and determine the maximum log10 change

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 11.2.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.2.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS, R, WinBUGS and WinNonLin software will be used.
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & AdaM IG Version 1.0 • For creation of AdaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented in SDTM.
Generation of RTF Files
• RTF files will be generated.

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for

Reporting Standards	
reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	sample size, mean, median, standard deviation, minimum, and maximum
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log-transformed data and between geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) – 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	t_{max}, %AUC_{ex}, t_{lag}, λ_z, λ_z lower, λ_z upper, λ_z no. of points
Listings	Interval, number of observations included in calculation of λ_z, regression coefficient and percent AUC extrapolated (%AUC_{ex})
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.3. Appendix 3: Derived and Transformed Data

11.3.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomization date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date
  • Ref Data ≥ Randomization Date → Study Day = Ref Date – (Randomization Date) + 1

11.3.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: Cumulative Dose = Sum of (Number of Days x Total Daily Dose) • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1

11.3.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcB is machine read & QTcF is not provided, then: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as: $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1

11.3.4. Pharmacokinetic

- 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).
- Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

PK Concentrations and Parameters

- **How to handle values below the quantification limit for the calculation of individual pharmacokinetic profiles**

If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For semilogarithmic log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots.

If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).

NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and from the individual subject plots. In some circumstances, there may be a pharmacokinetic rationale for fluctuation resulting in non-measurable concentrations in the middle of the concentration-time profile (e.g., entero-hepatic recycling, erratic absorption from transdermal/inhaled formulations). In these cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) and subsequent valid concentrations may be retained. A reference line indicating LLQ would then be included in plots.

For the calculation of mean or median pharmacokinetic profiles

When estimating the mean or median value for the concentration at a given time point (i.e., descriptive mean or median curve), the following guidelines should be considered: All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or median profiles. Measurable concentrations which follow more than one consecutive mid-profile NQ will be omitted (set to missing).

The mean/median value at a time-point where one or more samples have NQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the LLQ of the assay. For linear plots, zero concentration value(s) will be included in the plot. For semilogarithmic log-linear plots, zero concentration value(s) will be assigned a missing value. Zero mean or median values will be included in summary tables.

In certain cases, the NQ values could be set to missing or to some other values (e.g., ½ LLQ) with

- 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).
- Derived ISIS 505358 plasma PK parameters including, but not limited to AUC, C_{max}, t_{max}, and $t_{½}$.

proper scientific justification(s). A reference line indicating LLQ would then be included in plots.

It should be noted that a high proportion of NQ values may affect the standard deviation (SD); if more than 30% of values are imputed, then SD will not be displayed. Any table of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of subjects with non-missing values) and number imputed (number of subjects with imputed values (i.e., NQ assigned zero concentration). BQL (Below the Quantification Limit) may be displayed in listings by legacy systems instead of NQ; these abbreviations are interchangeable and mean that a sample has been received, analysed and a concentration below the LLQ of the assay found.

Scientific judgement and prior knowledge should always be used in applying these guidelines.

How to Handle Anomalous Concentration Values
Individual concentrations deemed to be anomalous will be excluded from the pharmacokinetic analysis and median and mean profiles; such anomalous values will be identified (e.g., flagged by an asterisk or an appropriate footnote) in the data listings of the study report. Anomalous values are those that are inconsistent with known or expected pharmacokinetic behaviour of the drug, and are not defined in a statistical outlier sense. Clear justification must be provided in the report for exclusion of any data. Individual plasma concentration-time profiles by actual time and median/mean profiles by treatment (dose) by nominal time will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e., a linear plot) and one plot on the $\log_e$-transformed scale (i.e., semilogarithmic log-linear plot). In addition, a plot showing all individual subjects for each treatment (dose) will be produced (both linear and semilogarithmic log-linear).

11.3.5. Pharmacodynamic

- Correlation between GSK3389404 PK parameters and PD parameters, including HBV DNA (as appropriate), HbsAg, and HbeAg levels (as appropriate, HbeAg-positive subjects).
- Correlation between PD parameters, including HBV DNA, HBV RNA, HbsAg, and/or hepatitis B core related antigen (HbcrAg).

PD Values and Parameters

- HBV DNA (as appropriate), HBV RNA, HbsAg, HbeAg and HbcrAg levels that are below the LLOQ will be imputed as LLOQ – 1.
- In the scenario of multiple BLQ values, the Time to Nadir will be to the first BLQ value.

11.4. Appendix 4: Premature Withdrawals & Handling of Missing Data

11.4.1. Premature Withdrawals

Element	Reporting Detail

General	• Subject study completion (i.e. as specified in the protocol) was defined as below:
	  ○ 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.
	• Withdrawn subjects will be replaced in Part 1 but not be replaced in Part 2.
	• All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.4.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.4.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix

Element	Reporting Detail
	1: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

11.4.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these results in a date prior to Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. ○ The AE will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

11.5. Appendix 5: Values of Potential Clinical Importance

11.5.1. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

11.5.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

11.6. Appendix 6: Model Checking and Diagnostics for Statistical Analyses

11.6.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints AUC and C_{max}
Analysis	• Mixed effects
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.	

11.7. Appendix 7: Pharmacokinetic Analyses

11.7.1. Dose Proportionality

Dose proportionality of GSK3389404 and ISIS 505358 following single-dose administration in Part 1 will be studied using the power model

$$y = \alpha \times (dose)^{\beta}$$

where y denotes the PK parameter being analyzed [$AUC_{(0-\infty)}$, C_{max}, C_{24} for Part 1].
Dose proportionality implies that β = 1 and will be assessed by estimating β along with its 90% confidence interval. The exponent, β, in the power model will be estimated by regressing the log_e-transformed PK parameter on log_e-transformed dose.

$$\text{Log}(y)=\log(\alpha) + \beta * \log(dose)$$

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed, with subject as a random effect or a fixed effect power model will be fitted. The mean slope will be estimated from the power model and the corresponding 90% confidence interval calculated. Point estimates and confidence intervals for the slope will be reported to 4 decimal places with no rounding.

```
An example of SAS code is included here for the power model approach.

ODS output solution=stat
Proc Mixed;
      class subject;
      model logPKvar = logdose /cl alpha=0.1 solution;
run;
```

If the power model does not show dose proportionality then pairwise analysis of variance (ANOVA) may be used as an exploratory analysis to understand the dose where dose proportionality fails. PK parameters will be normalized to the reference dose (30 mg for Part 1) and then log-transformed prior to the analysis. Dose will be treated as a categorical variable. Point estimates and 90% confidence intervals for AUC and C_{max} will be reported to 4 decimal places with no rounding.

```
An example of SAS code is also included here for the ANOVA approach.

ODS output solution=stat;
Proc Mixed;
      class subject treatment; /* treatments are different dose groups
      */
      model logdnPKvar = treatment/cl alpha=0.1 solution;;
      lsmeans treatment; /* assuming one ref and three test treatments
      */
      estimate 'test1 vs ref' treatment -1 1 0 0 /cl alpha=0.1;
      estimate 'test2 vs ref' treatment -1 0 1 0 /cl alpha=0.1;
run;
```

11.8. Appendix 8: Abbreviations & Trade Marks

11.8.1. Abbreviations

Abbreviation	Description
λ_z	Apparent terminal rate constant
$\%AUC_{ex}$	The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
AdaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AUC	Area under the concentration-time
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post-dose
$AUC_{(0-8)}$	Area under the concentration-time curve from time zero to 8 hours post-dose
A&R	Analysis and Reporting
C_{24}	Concentration in the plasma at 24 hours after dosing
CDISC	Clinical Data Interchange Standards Consortium
Change from Baseline to Nadir	Maximum observed change from baseline pharmacodynamic value, i.e. minimum absolute value
CI	Confidence Interval
CL/F	Apparent subcutaneous plasma clearance after extravascular
C_{max}	Maximum observed concentration in plasma
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance

Abbreviation	Description
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
Nadir	Minimum observed pharmacodynamic value
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
$t_{½}$	Apparent terminal half-life
TA	Therapeutic Area
Time to Nadir	Time to reach Nadir
TFL	Tables, Figures & Listings
t_{lag}	Lag time before observation of quantifiable concentrations in plasma
t_{max}	Time to reach C_{max}
GSK	GlaxoSmithKline

11.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

11.9. Appendix 9: List of Data Displays

11.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population (Part 1)	1.01 to 1.12	N/A
Safety (Part 1)	3.01 to 3.20	3.01 to 3.07
Pharmacokinetic (Part 1)	4.01 to 4.10	4.01 to 4.05
Pharmacodynamic (Part 1)	5.01 to 5.04	5.01 to 5.16
Section	**Listings**	
ICH Listings	1.01 to 3.51	
Other Listings	4.01 to 5.03	

11.9.2. Table of Contents of Data Display

11.9.2.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.01	[ITT]	ES1	Summary of Subject Disposition (Part 1)		SAC [1]
1.02	[Screened Population]	ES6	Summary of Screening Status and Reasons for Screening Failure (Part 1)		SAC [1]
1.03	[Screened Population]	NS1	Summary of Enrolled Subjects by Country and Site ID (Part 1)		SAC [1]
1.04	[ITT]	DV1	Summary of Important Protocol Deviations (Part 1)		SAC [1]
1.05	[ITT]	DM1	Summary of Demographic Characteristics (Part 1)		SAC [1]
1.06	[ITT]	DM1	Summary of Baseline Disease Characteristics (Part 1)		SAC [1]
1.07	[ITT]	DM11	Summary of Age Ranges (Part 1)		SAC [1]
1.08	[ITT]	DM5	Summary of Race and Racial Combinations (Part 1)		SAC [1]
1.09	[ITT]	MH4	Summary of Medical Conditions (Part 1)		SAC [1]
1.10	[ITT]	CM1	Summary of Prior Medications (Part 1)		SAC [1]
1.11	[ITT]	CM1	Summary of Concomitant Medications (Part 1)		SAC [1]
1.12	[ITT]	CM1	Summary of Baseline Nucleocide Use (Part 1)		SAC [1]

11.9.2.2. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.01	[Safety]	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade (Part 1)		SAC [1]
3.02	[Safety]	AE5B	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade (Part 1)		SAC [1]
3.03	[Safety]	AE5B	Summary of Non-Serious Adverse Events by System Organ Class and Preferred Term and maximum Grade (Part 1)		SAC [1]
3.04	[Safety]	AE3	Summary of Adverse Events by Overall Frequency (Part 1)		SAC [1]
3.05	[Safety]	AE3	Summary of Grade 2-4 Adverse Events by Overall Frequency (Part 1)		SAC [1]
3.06	[Safety]	AE3	Summary of Drug-Related Grade 2-4 Adverse Events by Overall Frequency (Part 1)		SAC [1]
3.07	[Safety]		Overall Summary of Adverse Events and Lab Abnormalities (Part 1)		SAC [1]
Lab					
3.08	[Safety]	LB1	Summary of Chemistry Changes from Baseline by Visit (Part 1)		SAC [1]
3.09	[Safety]		Summary of Chemistry Maximum Grade by Category (Part 1)		SAC [1]
3.10	[Safety]	LB1	Summary of Hematology Changes from Baseline by Visit (Part 1)		SAC [1]
3.11	[Safety]		Summary of Hematology Maximum Grade by Category (Part 1)		SAC [1]
3.12	[Safety]	LB1	Summary of Urinalysis Changes from Baseline by Visit (Part 1)		SAC [1]
3.13	[Safety]	LB2	Summary of Coagulation Lab Data (Part 1)		SAC [1]
3.14	[Safety]		Summary of Complement Product Levels after Study Drug Dose (Part 1)		SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
3.15	[Safety]	EG1	Summary of ECG Findings (Part 1)		SAC [1]
3.16	[Safety]	EG2	Summary of ECG Changes from Baseline by Visit (Part 1)		SAC [1]
3.17	[Safety]	CP_EG11	Summary of Maximum Emergent QTc Values by Category (Part 1)		SAC [1]
3.18	[Safety]	CP_EG12	Summary of Maximum Change from Baseline in QTc Values by Category (Part 1)		SAC [1]
Vital Signs					
3.19	[Safety]	VS1	Summary of Vital Sign Changes from Baseline by Visit (Part 1)		SAC [1]
3.20	[Safety]		Summary of Vital Sign Values by Category (Part 1)		SAC [1]

11.9.2.3. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Lab					
3.1.	[Safety]	LIVER9	Scatter Plot of Maximum vs. Baseline for ALT (Part 1)		SAC [1]
3.2.	[Safety]	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin (Part 1)		SAC [1]
3.3.	[Safety]		Mean Plot of Liver Functions (Part 1)		SAC [1]
3.4.	[Safety]		Individual Line Plot of Liver Functions (Part 1)		SAC [1]
3.5.	[Safety]		Mean Plot of Coagulation Tests (Part 1)		SAC [1]
3.6.	[Safety]		Individual Line Plot of Coagulation Tests (Part 1)		SAC [1]

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	[Safety]		Individual Line Plot of Chemistry Lab Tests (Part 1)		SAC [1]

11.9.2.4. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.01	[PK]	PK01	Summary of GSK3389404 Plasma Pharmacokinetic Concentration-Time Data [ng/mL] by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.02	[PK]	PK01	Summary of ISIS 505358 Plasma Pharmacokinetic Concentration-Time Data [ng/mL] by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.03	[PK]	PK03	Summary of Derived GSK3389404 Plasma Pharmacokinetic Parameters by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.04	[PK]	PK03	Summary of Derived ISIS 505358 Plasma Pharmacokinetic Parameters by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.05	[PK]	PK05	Summary of Log-Transformed Derived GSK3389404 Plasma Pharmacokinetic Parameters by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.06	[PK]	PK05	Summary of Log-Transformed Derived ISIS 505358 Plasma Pharmacokinetic Parameters by Treatment Group and HBeAg Status in Part 1		SAC [1]
4.07	[PK]	PK_T1	Assessment of Dose Proportionality of GSK3389404 Following Single Dose in Part 1		SAC [1]
4.08	[PK]	PK_T1	Assessment of Dose Proportionality of ISIS 505358 Following Single Dose in Part 1		SAC [1]

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.09	[PK]	PK_T4	Summary of Results of Dose Proportionality Assessment of GSK3389404 using ANOVA Following Single Dose in Part 1		SAC [1]
4.10	[PK]	PK_T4	Summary of Results of Dose Proportionality Assessment of ISIS 505358 using ANOVA Following Single Dose in Part 1		SAC [1]

11.9.2.5. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.01	[PK]	PK17	Mean (+SD) GSK3389404 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status - Part 1 (Linear and Semi-Log)		SAC [1]
4.02	[PK]	PK17	Mean (+SD) ISIS 505358 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status - Part 1 (Linear and Semi-Log)		SAC [1]
4.03	[PK]	PK18	Median (range) GSK3389404 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status - Part 1 (Linear and Semi-Log)		SAC [1]
4.04	[PK]	PK18	Median ISIS 505358 Plasma Concentration-Time Plot by Treatment Group and HBeAg Status - Part 1 (Linear and Semi-Log)		SAC [1]
4.05	[PK]	PK16a	Individual GSK3389404 and ISIS 505358 Plasma Concentration-Time Plot – Part 1 (Linear and Semi-Log)		SAC [1]

11.9.2.6. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.01	[PD]	PK01	Summary of Pharmacodynamic Absolute Value-Time Data by Treatment Group and HBeAg Status		SAC [1]
5.02	[PD]	PK01	Summary of Pharmacodynamic Log10 Absolute Value-Time Data by Treatment Group and HBeAg Status		SAC [1]
5.03	[PD]	PK01	Summary of Pharmacodynamic Log10 Change from Baseline Value-Time Data by Treatment Group and HBeAg Status		SAC [1]
5.04	[PD]	PK03	Summary of Nadir and Time to Nadir by Treatment Group and HBeAg Status		SAC [1]
5.05	[PD]	PK03	Summary of Log10 Change from Baseline to Nadir by Treatment Group and HBeAg Status		SAC [1]

11.9.2.7. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.01	[PD]	PK17	Mean (+SD) Pharmacodynamic Absolute Value-Time Plot by Treatment Group and HBeAg Status		SAC [1]
5.02	[PD]	PK17	Mean (+SD) Pharmacodynamic Log10 Change from Baseline Value-Time Plot by Treatment Group and HBeAg Status		SAC [1]
5.03	[PD]	PK18	Median (range) Pharmacodynamic Absolute Value-Time Plot by Treatment Group and HBeAg Status		SAC [1]
5.04	[PD]	PK18	Median (range) Pharmacodynamic Log10 Change from Baseline Value-Time Plot by Treatment Group and HBeAg Status		SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.05	[PD]	PK16a	Individual Pharmacodynamic Absolute Value-Time Plot (Log10 scale)		SAC [1]
5.06	[PD]	PK16a	Individual Pharmacodynamic Log10 Change from Baseline Value-Time Plot		SAC [1]
5.07	[PD]		Mean (+SD) Pharmacodynamic Absolute Value-Time Plot by Treatment Group		SAC [1]
5.08	[PD]		Mean (+SD) Pharmacodynamic Log10 Change from Baseline Value-Time Plot by Treatment Group		SAC [1]
5.09	[PD]		Scatter Plot of Nadir versus AUC(0-inf) for GSK3389404		SAC [1]
5.10	[PD]		Scatter Plot of Time to Nadir versus AUC(0-inf) for GSK3389404		SAC [1]
5.11	[PD]		Scatter Plot of Log10 Change from Baseline to Nadir versus AUC(0-inf) for GSK3389404		SAC [1]
5.12	[PD]		Scatter Plot of Nadir versus Cmax for GSK3389404		SAC [1]
5.13	[PD]		Scatter Plot of Time to Nadir versus Cmax for GSK3389404		SAC [1]
5.14	[PD]		Scatter Plot of Log10 Change from Baseline to Nadir versus Cmax for GSK3389404		SAC [1]
5.15	[PD]		Individual Plot of HBsAg, HBV DNA, and HBeAg Values and ALT Values		SAC [1]
5.16	[PD]		Individual Plot of HBsAg, HBV DNA, and HBeAg Log10 Change from Baseline Values and ALT Values		SAC [1]

11.9.2.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
1.01	[Screened Population]	ES7	Listing of Reasons for Screen Failure (Part 1)		SAC [1]
1.02	[ITT]	ES2	Listing of Reasons for Study Withdrawal (Part 1)		SAC [1]
1.03	[ITT]	BL1	Listing of Subjects for whom Treatment Blind was Broken During the Study (Part 1)		SAC [1]
1.04	[ITT]	TA1	Listing of Randomized and Actual Treatments (Part 1)		SAC [1]
1.05	[ITT]	DV2	Listing of Protocol Deviations (Part 1)		SAC [1]
1.06	[ITT]	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations (Part 1)		SAC [1]
1.07	[ITT]	SP3	Listing of Subjects Excluded from Any Population (Part 1)		SAC [1]
1.08	[ITT]	DM2	Listing of Demographic Characteristics (Part 1)		SAC [1]
1.09	[ITT]	DM9	Listing of Race (Part 1)		SAC [1]
1.10	[ITT]	CM2	Listing of Prior and Concomitant Medications (Part 1)		SAC [1]
1.11	[ITT]	CM2	Listing of Baseline Nucleocide Use (Part 1)		SAC [1]
1.12	[ITT]	MH2	Listing of Medical Conditions (Part 1)		SAC [1]
Exposure					
3.01	[Safety]	EX3	Listing of Exposure Data (Part 1)		SAC [1]
Adverse Events					
3.02	[Safety]	AE8	Listing of All Adverse Events (Part 1)		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.03	[Safety]	AE7	Listing of Subject Numbers for Specified Adverse Events (Part 1)		SAC [1]
3.04	[Safety]	AE2	Listing of Relatioship between System Organ Class and Verbatim Text (Part 1)		SAC [1]
3.05	[Safety]	AE8	Listing of Non-Fatal Serious Adverse Events (Part 1)		SAC [1]
3.06	[Safety]	AE8	Listing of Fatal Serious Adverse Events (Part 1)		SAC [1]
3.07	[Safety]	AE8	Listing of Adverse Events Leading to Withdrawal from Study (Part 1)		SAC [1]
Lab					
3.11	[Safety]	LB5	Listing of All Laboratory Data (Part 1)		SAC [1]
3.12	[Safety]	LB5	Listing of All Laboratory Data for Subjects with any Grade 1 higher Abnormality (Part 1)		SAC [1]
3.13	[Safety]	LB5	Listing of All Laboratory Data with Grade 1 or Higher (Part 1)		SAC [1]
ECG					
3.21	[Safety]	CP_EG3	Listing of All ECG Data (Part 1)		SAC [1]
3.22	[Safety]	CP_EG3	Listing of All ECG Data for Subjects with Any Value of Potential clinical Importance (Part 1)		SAC [1]
3.23	[Safety]		Listing of All ECG Findings (Part 1)		SAC [1]
3.23	[Safety]	CP_EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding (Part 1)		SAC [1]
Vital Signs					
3.31	[Safety]	CP_VS4	Listing of All Vital Signs (Part 1)		SAC [1]
3.32	[Safety]	CP_VS4	Listing of All Vital Signs for Subjects with Any Values of Potential Clinical Importance (Part 1)		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Liver					
3.41	[Safety]	LIVER5	Listing of Liver Stopping/Monitoring Event Reporting (Part 1)		SAC [1]
Death					
3.51	[Safety]		Listing of Deaths (Part 1)		SAC [1]

11.9.2.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.01	[PK]	PK08	Listing of GSK3389404 Plasma Pharmacokinetic Concentration-Time Data by Study Part, Cohort, and Study Day		SAC [1]
4.02	[PK]	PK08	Listing of ISIS 505358 Plasma Pharmacokinetic Concentration-Time Data by Study Part, Cohort, and Study Day		SAC [1]
4.03	[PK]	PK14	Listing of Derived GSK3389404 Plasma Pharmacokinetic Parameters for Each Cohort in Part 1		SAC [1]
4.04	[PK]	PK14	Listing of Derived ISIS 505358 Plasma Pharmacokinetic Parameters for Each Cohort in Part 1		SAC [1]
4.05	[PK]	PK14	Individual GSK3389404 Plasma Lambda_z Related Pharmacokinetic Parameters for Each Cohort in Part 1		SAC [1]
4.06	[PK]	PK14	Individual ISIS 505358 Plasma Lambda_z Related Pharmacokinetic Parameters for Each Cohort in Part 1		SAC [1]
4.07	[PK]	Non-Standard PK L_1	Individual GSK3389404 Plasma Concentrations (ng/mL) by Scheduled Time in Part 1		SAC [1]
4.08	[PK]	Non-Standard PK L_1	Individual ISIS 505358 Plasma Concentrations (ng/mL) by Scheduled Time in Part 1		SAC [1]
PD					
5.01	[PD]	PK08	Listing of Pharmacodynamic Absolute, Log10 Absolute, and Log10 Change from Baseline Value-Time Data by Cohort and Study Day		SAC [1]
5.02	[PD]	PK14	Listing of Derived Pharmacodynamic Parameters Nadir, Time to Nadir, and Log10 Change from Baseline to Nadir for Each Cohort		SAC [1]

11.9.3. Mock Example Shell Referencing

Mock shell will be in a separate document.