Reporting and Analysis Plan

Study ID: 212548

Official Title of Study: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants

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Title	:	Reporting and Analysis Plan for Study 212548: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants
Compound Number	:	VH3739937 (also known as GSK3739937)
Clinical Study Identifier	:	212548
Effective Date	:	Refer to Document date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 212548
- This RAP is intended to describe the safety, tolerability, and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

1. INTRODUCTION 6

2. SUMMARY OF KEY PROTOCOL INFORMATION 7
   2.1. Changes to the Protocol Defined Statistical Analysis Plan 7
   2.2. Study Objective(s) and Estimand(s) / Endpoint(s) 7
   2.3. Study Design 10
   2.4. Statistical Analyses 13
      2.4.1. Part 1 (SAD) and 2 (MAD) 13
      2.4.2. Part 3 (RBA) 13

3. PLANNED ANALYSES 14
   3.1. Interim Analyses 14
   3.2. Final Analyses 14

4. ANALYSIS POPULATIONS 15
   4.1. Protocol Deviations 15

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS 16
   5.1. Study Treatment & Sub-group Display Descriptors 16
   5.2. Baseline Definitions 17
   5.3. Other Considerations for Data Analyses and Data Handling Conventions 18

6. STUDY POPULATION ANALYSES 19
   6.1. Overview of Planned Study Population Analyses 19

7. SAFETY ANALYSES 20
   7.1. Adverse Events Analyses 20
   7.2. Clinical Laboratory Analyses 20
   7.3. Other Safety Analyses 21

8. PHARMACOKINETIC ANALYSES 22
   8.1. Primary Pharmacokinetic Analyses 22
      8.1.1. Endpoint / Variables 22
         8.1.1.1. Drug Concentration Measures 22
         8.1.1.2. Derived Pharmacokinetic Parameters 22
      8.1.2. Summary Measure 23
      8.1.3. Population of Interest 24
      8.1.4. Strategy for Intercurrent (Post-Randomization) Events 24
      8.1.5. Statistical Analyses / Methods 24
         8.1.5.1. Statistical Methodology Specification 24
            8.1.5.1.1. Dose Proportionality (Power Model) 24
            8.1.5.1.2. Accumulation Ratio 25
            8.1.5.1.3. Assessment of Steady State 27
            8.1.5.1.4. Relative Bioavailability and Food Effect 28
   8.2. Exploratory Pharmacokinetic Analyses 29

9. POPULATION PHARMACOKINETIC (POPPK) ANALYSES 30

10. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES 31

11. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC 32
11.1. Study Population 32
11.1.1. Subject Disposition 32
11.1.2. Protocol Deviations 32
11.1.3. Additional Displays for Participants with a COVID-19 Infection 32
11.2. Safety 32
11.2.1. Assessment of COVID-19 AEs 32
11.2.2. Impact of COVID-19 Pandemic on Safety Results 32

12. REFERENCES 33

13. APPENDICES 34
13.1. Appendix 1: Exclusions from Analysis Populations 34
13.2. Appendix 2: Schedule of Activities 35
13.2.1. Protocol Defined Schedule of Events 35
13.3. Appendix 3: Assessment Windows 36
13.3.1. Definitions of Assessment Windows for Analyses 36
13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events 37
13.4.1. Study Phases 37
13.4.1.1. Study Phases for Concomitant Medication 37
13.4.2. Treatment Emergent Flag for Adverse Events 37
13.5. Appendix 5: Data Display Standards & Handling Conventions 38
13.5.1. Reporting Process 38
13.5.2. Reporting Standards 38
13.5.3. Reporting Standards for Pharmacokinetic 39
13.6. Appendix 6: Derived and Transformed Data 40
13.6.1. General 40
13.6.2. Study Population 40
13.6.3. Safety 40
13.6.4. Pharmacokinetic 41
13.6.5. Pharmacodynamic 41
13.6.6. Laboratory 41
13.7. Appendix 7: Reporting Standards for Missing Data 42
13.7.1. Premature Withdrawals 42
13.7.2. Handling of Missing Data 42
13.7.2.1. Handling of Missing and Partial Dates 42
13.8. Appendix 8: Values of Potential Clinical Importance 44
13.8.1. Laboratory Values 44
13.8.2. Urinalysis Values 44
13.8.3. ECG 44
13.8.4. Vital Signs 45
13.9. Appendix 9: Abbreviations & Trade Marks 46
13.9.1. Abbreviations 46
13.9.2. Trademarks 47
13.10. Appendix 10: List of Data Displays 48
13.10.1. Data Display Numbering 48

13.10.2. Mock Example Shell Referencing 48
13.10.3. Deliverables 48
13.10.4. Study Population Tables 49
13.10.5. Safety Tables 53
13.10.6. Pharmacokinetic Tables 59
13.10.7. Pharmacokinetic Figures 62
13.10.8. ICH Listings 68
13.10.9. Non-ICH Listings 70
13.11. Appendix 11: Example Mock Shells for Data Displays 72

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 Protocol: 212548/02. Note that GSK3739937 is also known as VH3739937 and will be referred to as VH3739937 for the remainder of this document.

Protocol Revision Chronology:		
212548/00	20-APR-2020	Original
212548/01	11-JUN-2020	Amendment 01 was generated to remove Sodium Stearyl Fumarate from the placebo formulation, to clarify administration for study interventions and maintenance of the blind. Revisions were made to the study eligibility criteria and safety assessments in response to the FDA's feedback and to mitigate the potential risks for study conduct during the COVID-19 pandemic. Given the absence of benefit to study participants, the exclusion criteria and the criteria for individual subject discontinuation, dose escalation and stopping the study were revised to be more conservative. Revisions were made to improve accuracy of the study risk assessment and the pharmacokinetic analyses.
212548/02	16-MAR-2021	Updates made following acquisition of clinical pharmacology data in Part 1, the Single Ascending Dose (SAD) 10 mg, 30 mg, 80 mg, 160 mg, 320 mg and 640mg treatment periods and Multiple Ascending Dose (MAD) Cohort 3; 25 mg to: • extend the period of post dosing assessment to include outpatient visits in the study; • include a higher dose SAD treatment period (800 mg); • revise the duration of dosing in MAD Cohort 5 (100 mg); and • inclusion of an additional MAD Cohort 6 (500 mg) to evaluate weekly oral dosing. Part 3 of the study was included to evaluate the relative bioavailability (RBA) of

		VH3739937 when administered as VH3739937 powder-in-a-bottle (PiB) or as VH3739937 100 mg Tablet under fasted and fed (moderate fat) conditions.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in most recent version of the protocol Amendment 2 (212548/02) [(Dated: 16-Mar-2021)] which introduced Part 3 (relative bioavailability and food effect).

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the safety and tolerability of VH3739937 following single and repeated daily and weekly oral administration in healthy participants (Part 1 & 2) • To assess the safety and tolerability of VH3739937 following single oral administration in healthy participants under fasted or fed (moderate calorie and fat) conditions (Part 3) • To evaluate the relative bioavailability (RBA) of VH3739937 powder in bottle (PiB) versus VH3739937 tablet and the effect of food on the PK of VH3739937 tablets and VH3739937 PiB (Part 3)	VH3739937 safety parameters: • Adverse events; post baseline values and changes over time of clinical laboratory evaluations (haematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values (Part 1, 2, and 3) • Derived PK parameters for VH3739937, as data permits: Part 3 (single dose): $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max},
Secondary Objectives	**Secondary Endpoints**
• To describe the PK profile of VH3739937 following single (Part 1 and 3) and repeated daily and weekly oral administration in healthy participants (Part 2), as data permits	Derived PK parameters for VH3739937, as data permits: • Part 1 (single dose): $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F • Part 2 (repeated once daily [QD] dose):

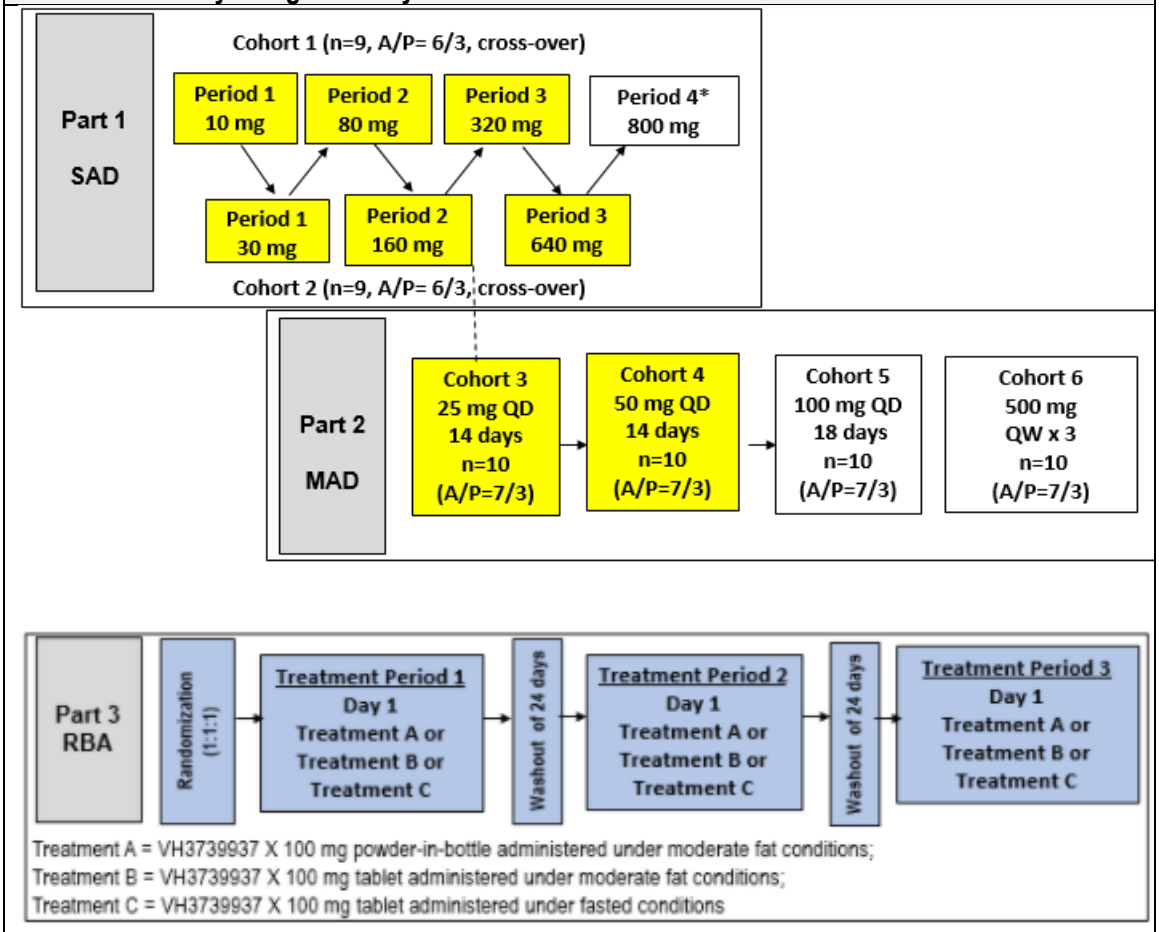
Objectives	Endpoints
	○ Day 1: AUC $_{(0\text{-}24)}$, C_{max}, C_{24}, t_{max}, t_{lag} ○ Day 14 (Cohorts 3 and 4): $AUC_{(0\text{-}\tau)}$, C_{max}, $C\tau$, t_{max}, $t_{1/2}$, and CL/F ○ Day 14 (Cohort 5): $AUC_{(0\text{-}\tau)}$, C_{max}, $C\tau$, t_{max} ○ Day 18 (Cohort 5): $AUC_{(0\text{-}\tau)}$, C_{max}, $C\tau$, t_{max}, $t_{1/2}$, and CL/F • Part 2 (repeated once weekly [QW] dose, as data permits: ○ Day 1 (Cohort 6): AUC $_{(0\text{-}168)}$, C_{max}, C_{168}, t_{max}, t_{lag} ○ Day 8 (Cohort 6): AUC $_{(0\text{-}168)}$, C_{max}, C_{168}, t_{max} ○ Day 15 (Cohort 6): $AUC_{(0\text{-}t)}$, C_{max}, $C\tau$,, t_{max}, $t_{1/2}$, and CL/F • Part 3 (single dose): AUC $_{(0\text{-}24)}$, $AUC_{(0\text{-}inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F
• To examine dose proportionality following single and repeated doses of VH3739937 (Part 1 & 2), as data permits	Derived PK parameters for VH3739937, as data permits: • Part 1 (single dose): $AUC_{(0\text{-}inf)}$, C_{max}. • Part 2 (repeated dose): $AUC_{(0\text{-}\tau)}$, C_{max}, $C\tau$
• To predict the accumulation from single dose data (Part 1) and assess accumulation of VH3739937 after repeat doses (Part 2 at steady state), as data permits	Accumulation indices for PK parameters for VH3739937, as data permits: • Part 1 (single dose): predicted accumulation ratio Rp based on AUC • Part 2 (repeated dose): observed accumulation ratios: RAUC(0-τ) , R(Cmax), R($C\tau$)
• To assess time to steady-state of VH3739937 (Part 2)	Derived PK parameters for VH3739937, as data permits: • Part 2 (repeated dose): ○ Cohorts 3 and 4: Pre-dose concentrations on Day 2-14 ○ Cohort 5: Pre-dose concentrations on Day 2-18
Exploratory Objectives	**Exploratory Endpoints**
• To assess the exposure response relationship between VH3739937 and safety parameter, including QTcF following single and repeated administration (Part 1 & 2)	• Change-from-baseline QTcF (ΔQTcF)

Objectives	Endpoints
• To collect plasma and urine samples for analysis of metabolites of VH3739937	• Metabolites of VH3739937 in plasma and urine. The analyses will be conducted and reported separately from this protocol.
• To characterize renal excretion of VH3739937, as data permits	• Urinary recovery of VH3739937 (Ae[0-x]), Ae[0-τ] and Ae[0-t]) and renal clearance (CLr)
• To collect duodenal bile for analysis of metabolites of VH3739937 (Part 2, Cohort 5 only)	• Metabolites of VH3739937 in duodenal bile. The analyses will be conducted and reported separately from this protocol

• Note: The exploratory endpoints may be analyzed once VH3739937 clinical development continues.

2.3. Study Design

Overview of Study Design and Key Features



Note: Box color has no interpretation

Design Features	• This is a three-part, Phase 1, double-blind (sponsor-unblinded), randomized, placebo controlled, single- and repeat-dose escalation study and relative bioavailability/food effect study. **Part 1 (SAD):** • The SAD portion of the study will be conducted in an interlocking crossover fashion with two separate cohorts of 9 healthy participants each. Each of these two cohorts may contain a minimum of three escalating doses of VH3739937 through to 800mg • In each escalating period and Cohort, 6 participants will be randomized to VH3739937 and 3 participants will be randomized to placebo. • Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses with 3-period crossover, placebo-controlled. • To reduce operational complexity, the 800 mg SAD dose will use new participants who were not exposed to previous lower doses of VH3739937 **Part 2 (MAD):** • Part 2 consists of approximately 3 ascending repeat-dose daily administration cohorts (Cohorts 3 to 5), and one repeat-dose weekly administration cohort (Cohort 6) each with 10 participants who will receive a once-daily dose of VH3739937 or

Overview of Study Design and Key Features	
	placebo (PBO) for 14 consecutive days (cohorts 3 and 4), or for 18 consecutive days (cohort 5). Participants in Cohort 6 will receive one dose per week for 3 consecutive weeks. • The duration of dosing in Cohort 5 is to support up to 18-day dosing as an oral lead in for the future SAD and MAD studies of the long acting formulation of VH3739937. This duration is to potentially allow the identification of any early drug hypersensitivity reactions (HSR) which may occur before the administration of the long acting formulation. • In each escalating dose cohort, 7 participants will be randomized to receive VH3739937 and 3 participants will be randomized to receive PBO **Part 3 (RBA/FE)** • Part 3 is a randomized, open-label, single-dose, 3-period crossover Cohort 7 to compare the RBA of the PiB formulation of VH3739937 with the tablet formulation and to assess the effect of food on the safety, tolerability and PK of the tablet formulation in healthy participants. • In Part 3, approximately 18 participants will be treated to ensure that 12 evaluable participants complete Cohort 7.
Dosing	**Part 1 (SAD):** • In Part 1 participants will receive a single dose of VH3739937 • Dose escalation in Part 1 will be determined by the Dose Escalation Committee based on the double-blind (sponsor-unblinded) safety data and the PK data from the current and previous dose(s). • Dose escalation will not exceed approximately 3-fold between doses up to approximately the predicted minimally effective dose and will not exceed 2-fold thereafter. • Dose escalation in Part 1 will require (from the current dosing group) at least 24 hours of safety and PK data from 4 participants receiving active drug. Dose escalation will be guided by safety and the SAD PK stopping criteria (see Protocol Section 8). • Due to the alternating dosing periods between Cohort 1 and Cohort 2, a participant in either cohort will receive the next dose after approximately 3 or 4 weeks. **Part 2 (MAD):** • In Part 2 participants will receive a single dose of VH3739937 each day for either 14 days (Cohorts 3 and 4) 18 days (Cohort 5), or once weekly for 3 weeks (Cohort 6) • Part 2 (MAD) of the study will be initiated once the single dose safety and preliminary PK data for the anticipated minimally effective dose has been evaluated in the SAD. • The potential minimally effective dose for VH3739937, noted as 25 mg, is anticipated to be that which is predicted to provide a steady state Ctrough ≥ 0.258μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1. • Dose escalation in Part 2 will be determined by the VH/GSK study team and the PI based on the double-blind (sponsor-unblinded) safety and PK data (minimally up to 24 h post Day 14 dose) from the current and previous dosing cohort(s). Specifically, 14 days of safety and PK data (minimally up to 24 h post Day 14 dose) from a minimum of five participants in current cohort receiving active drug will be required for dose escalation

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
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Part 3 (RBA/FE)

- Participants will receive each of the following treatments administered as 1 treatment per period:
  - Treatment A: VH3739937 PiB, 100 mg (single dose oral suspension of VH3739937 dispersion) administered under moderate fat conditions (reference)
  - Treatment B: VH3739937 Tablet, 100 mg (single dose given as a 100 mg tablet(s)) administered under moderate fat conditions (test)
  - Treatment C: VH3739937 Tablet, 100 mg (single dose given as 100 mg tablet(s)) administered under fasted conditions (reference).

- To ensure adequate washout, there will be at least 24 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 24 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

</td></tr>
<tr><td>Time & Events</td><td>

- Refer to Appendix 2: Schedule of Activities

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<tr><td>Treatment Assignment</td><td>

Part 1 (SAD):

- Participants in either Cohort 1 or Cohort 2 will be assigned to 1 of the 3 treatment sequences in a cross-over, and each participant will receive placebo once.

Cohort 1	Period 1	Period 2	Period 3
Sequence 1	Placebo	Dose 3	Dose 5
Sequence 2	Dose 1	Placebo	Dose 5
Sequence 3	Dose 1	Dose 3	Placebo

Cohort 2	Period 1	Period 2	Period 3
Sequence 1	Placebo	Dose 4	Dose 6
Sequence 2	Dose 2	Placebo	Dose 6
Sequence 3	Dose 2	Dose 4	Placebo

- When the 800 mg dose is evaluated, 9 new participants, who were not previously exposed to any dose of VH3739937 will be enrolled in the study. Six participants randomized to receive VH3739937 and 3 participants will be randomized to receive placebo.

Part 2 (MAD):

- In Cohorts 3 to 5, 10 participants per cohort (active/PBO=7/3) will receive a once-daily dose of VH3739937 or PBO for 14 days (Cohort 3 and 4) or 18 days (Cohort 5)
- In Cohort 6, 10 participants (active/PBO=7/3) will receive a once-weekly dose of 500 mg VH3739937 or PBO over the course of 14 days (Doses on Day 1, 8, and 15)

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Overview of Study Design and Key Features	

	Part 3 (RBA/FE):
	• In Part 3 participants will randomly be assigned to a receive a random sequence of the following treatments:
	  ○ Treatment A: VH3739937 PiB, 100 mg (administered as oral suspension under moderate fat conditions (reference)
	  ○ Treatment B: VH3739937 Tablet, 100 mg (single dose given as a 100 mg tablet(s)) administered under moderate fat conditions (test)
	  ○ Treatment C: VH3739937 Tablet, 100 mg (single dose given as 100 mg tablet(s)) administered under fasted conditions (reference)
	• In Part 3, participants will be assigned to one of three sequences according to a Latin square design. The three sequences are:
	  ○ A/B/C
	  ○ B/C/A
	  ○ C/A/B

Interim Analysis	• All preliminary safety, tolerability, and available PK data will be reviewed internally at ViiV/GSK prior to each dose escalation. Safety data (labs, vital signs, ECG, AEs, SAEs) will be reviewed by the PI/Sub-I and ViiV/GSK study team after completion of each dose level. • Dose escalation can only occur after DEC has found that the safety and PK profiles are supportive to proceed with the evaluation of the next higher dose level (See Protocol Section 4.3.6 Dose Escalation Committee).

2.4. Statistical Analyses

2.4.1. Part 1 (SAD) and 2 (MAD)

The main purpose of Parts 1 and 2 of study is to assess the safety, tolerability and PK of single and repeated oral doses of VH3739937 in healthy volunteers. A mixed model will be used to assess whether participants in Part 2 achieved steady state as described in Section 8.1.5.1.

2.4.2. Part 3 (RBA)

The purpose of Part 3 is to evaluate the relative bioavailability and food effect of two differing formulations of VH3739937 (tablet vs. powder in a bottle). For the assessment of relative bioavailability of formulation and food effect the log-transformed PK parameters will be analysed as data permits using separate mixed effect models with fixed effect terms for fed vs. fasted and tablet vs PiB. Participant will be treated as a random effect in each model. Point estimates and their associated 90% CIs will be calculated for the difference in $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}inf),}$ and C_{max} for the tablet vs PiB and fed vs fasted comparisons. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of tablet vs PiB and fed vs fasted in PK parameter values on the original scale.

No formal statistical hypothesis will be tested. The mixed model will be used to estimate relative bioavailability and food effect but will not be used to justify statistical bioequivalence.

3. PLANNED ANALYSES

3.1. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available pharmacokinetic data will be reviewed internally at the Dose Escalation Committee (ViiV/GSK) prior to each dose escalation or administration and according to the dose escalation charter. Safety data (labs, vital signs, ECG, AEs, SAEs) will be reviewed by the PI/Sub-I and ViiV/GSK study team after completion of each dose level. Dose escalation can only occur after PI/Sub-I and ViiV/GSK study team has found that the safety, PK profiles are supportive to proceed with the evaluation of the next highest dose level.

At each dose, the Bayesian probability of an individual exceeding the Cmax threshold in Part 1 and the Bayesian probability of an individual exceeding the AUC threshold in Part 2 will be calculated and compared with 50%. This will be used to help selection of the next dose together with safety and tolerability data. The Bayesian probability will be based on Whitehead's model shown below [Whitehead, 2001] using non-informative prior for model parameters.

$$y_{ij} = \theta_1 + \theta_2\, d_{ij} + s_i + \epsilon_{ij}$$

Where y_{ij} is log-PK of i-th participant to j-th dose, d_{ij} is j-th log-dose administered to i-th participant. θ_1 and θ_2 are population intercept and slope, respectively. s_i is random effect of i -th participant and ϵ_{ij} is random error of i -th participant in j-th dose.

When intra-participant variability cannot be estimated during PK predictions in Part 1 (i.e., early on in the study when there is not sufficient information to estimate intra-participant variability) and for conducting prediction of all doses in Part 2, the same Whitehead's model will be used for Bayesian probability calculations as below.

$$y_i = \theta_1 + \theta_2\, d_i + \epsilon_i$$

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

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
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.	• Study Population
Safety	• All randomized participants who received at least one dose of study treatment. • Participants will be analyzed according to the intervention they received.	• Study Population • Safety
Pharmacokinetic (PK)	• The PK Population will include all participants who undergo plasma or urine PK sampling and have evaluable PK assay results.	• PK analyses

Refer to Appendix 10 which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Separately, any important deviations which result in exclusion from analysis populations and events that result in exclusion from analysis populations will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan v1.0 June 2020

- 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 populations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment comparisons of relative bioavailability and food effect will be displayed as follows using the descriptors respectively:

1. (B vs. A): VH3739937 X 100 mg (single dose given as 100 mg tablet(s)) administered under moderate fat conditions (test) vs. VH3739937 X 100 mg (single dose oral suspension of VH3739937 dispersion) administered under moderate fat conditions (reference)
2. (B vs. C): VH3739937 X 100 mg (single dose given as 100 mg tablet(s)) administered under moderate fat conditions (test) vs. VH3739937 X 100 mg (single dose given as 100 mg tablet(s)) administered under fasted conditions (reference).

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
Part 1			
P	Placebo	SD PBO	1
D1	GSK3739937 Dose Level 1	SD 10mg	2
D2	GSK3739937 Dose Level 2	SD 30mg	3
D3	GSK3739937 Dose Level 3	SD 80mg	4
D4	GSK3739937 Dose Level 4	SD 160mg	5
D5	GSK3739937 Dose Level 5	SD 320mg	6
D6	GSK3739937 Dose Level 6	SD 640mg	7
D7	GSK3739937 Dose Level 7 800 mg	SD 800mg	8
Part 2			
RP	Placebo Repeated Dose	QD PBO	9
R1	GSK3739937 Repeat Dose Level 1	QD 25mg	10
R2	GSK3739937 Repeat Dose Level 2	QD 50mg	11
R3	GSK3739937 Repeat Dose Level 3	QD 100 mg	12
WP	Weekly Placebo	QW PBO	13
W1	GSK3739937 Weekly Repeat Dose 500 mg	QW 500mg	14
Part 3			
A	GSK3739937 PiB Fed 100 mg	PiB Fed	15
B	GSK3739937 Tablet Fed 100 mg	Tablet Fed	16
C	GSK3739937 Tablet Fasted 100 mg	Tablet Fasted	17

NOTES:

- Order represents treatments being presented in TFL, as appropriate.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Part 1 (SAD Cohorts 1 and 2)

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Lab	X	X		Day -1
ECG	X	X	X	Day 1 (Pre-Dose)
Vital Signs	X	X	X	Day 1 (Pre-Dose)

Part 2 (MAD Cohorts 3, 4, 5, and 6)

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Lab	X	X	X	Day 1 (Pre-Dose)
ECG	X	X	X	Day 1(Pre-Dose)
Vital Signs	X	X	X	Day 1 (Pre-Dose)

Part 3 (RBA/FE)

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Lab	X	X		Day -1
ECG	X	X	X	Day 1 (Pre-Dose)
Vital Signs	X	X	X	Day 1 (Pre-Dose)

On Day 1 triplicate pre-dose ECGs will be performed. The baseline for every ECG parameter will be calculated as the average of that parameter's values from the Day 1 pre-dose triplicate ECG reading

On Day 1 three readings of blood pressure and pulse will be taken. The first reading will be rejected. The average of the second and third readings (as recorded in the CRF) will serve as baseline.

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

For Part 3, baseline will be rederived for each period.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of participant'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. Details of the planned displays are presented in Appendix 10.

7. SAFETY ANALYSES

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

Safety data are the primary endpoints of the study, will be presented in tabular format and summarized descriptively accordingly to GSK's Integrated Data Standards Library (IDSL) standards.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10 Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. While VH3739937 does not have a defined list of AESI, the AESI for the similar compound GSK3640254 will be used for this study. Further details of specific SOCs and SMQs for AESI of GS3640254 are maintained by that compound's SRT. The list broadly includes the following items:

- QT prolongation
- GI intolerability/toxicity
- Psychiatric events
    - Suicidal ideation/behaviour
    - Depression
    - Bipolar disorder Psychosis
    - Anxiety
    - Sleep disorders
    - Nervous system disorders

The details of the planned displays are provided in Appendix 10

7.2. Clinical Laboratory Analyses

The safety analyses will be based on the Safety population, presented by treatment group unless otherwise specified.

The ADLB dataset will be used, which contains the data that is available at a particular timepoint, with no imputation for missing values, unless otherwise stated in Appendix 7.

Laboratory values, and change from baseline for haematology, clinical chemistry, and liver function parameters will be summarized by visit and by treatment group, based on GSK Core Data Standards. Laboratory values for haematology, clinical chemistry, liver function, and urinalysis will also be listed by subject. In addition, the worst-case results

post baseline relative to baseline relative to normal range will be reported for haematology, and clinical chemistry. The details of the planned displays are in Appendix 10

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10

For worst-case results post baseline relative to baseline for vital signs, the average of any triplicate measurement, if taken, will be considered.

8. PHARMACOKINETIC ANALYSES

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic population, unless otherwise specified.

As an overview, individual, mean and median plasma VH3739937 concentration-time profiles will be plotted by treatment and day (for MAD) (linear and semi-log profiles). PK sampling times will be related to the start of the dosing date/time. Actual sampling times will be used to calculate all non-compartmental pharmacokinetic parameters. Individual concentrations of VH3739937 in plasma will be listed and summarised by treatment and nominal time.

8.1. Primary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-24)	Area under the plasma concentration time curve from zero to 24 hrs
AUC(0-168)	Area under the plasma concentration time curve from zero to 168 hrs
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
%AUCex	The percentage of AUC (0-inf) obtained by extrapolation (%AUCex) will be calculated as: **[AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100**
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.
C_{24}	Concentration at 24 hours post-dose
C168	Concentration at 168 hours post-dose
C_{last}	Last quantifiable concentration

Parameter	Parameter Description
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
t_{max}	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
t_{lag}	Absorption lag time
t_{last}	Time of last quantifiable concentration
CL/F	Apparent oral clearance

NOTES:

- Additional parameters may be included as required.

All the derived parameters described above will be listed. For each of these parameters, except tmax and tlag, the following summary statistics will be calculated for each treatment group: n, arithmetic mean, standard deviation (SD), median, minimum, maximum, geometric mean with associated 95% CI, standard deviation of logarithmically transformed data, and the between-participant CV (%CVb) (where $\%CVb = 100*\sqrt{(\exp(SD^2)-1)}$ based on the geometric mean for the log-transformed PK parameters. For tmax and tlag, median, maximum, minimum, arithmetic mean and standard deviation will be calculated.

8.1.2. Summary Measure

The following PK parameters will be derived and summarized as data permits:

- Part 1 (single dose): $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F

- Part 2 (repeated once daily [QD] dose):
  - Day 1: $AUC_{(0-24)}$, C_{max}, C_{24}, t_{max}, t_{lag}
  - Day 14 (Cohorts 3 and 4): $AUC_{(0-t)}$, C_{max}, Cτ, t_{max}, $t_{1/2}$, and CL/F
  - Day 14 (Cohort 5): $AUC_{(0-\tau)}$, C_{max}, Cτ, t_{max}
  - Day 18 (Cohort 5): $AUC_{(0-t)}$, C_{max}, Cτ, t_{max}, $t_{1/2}$, and CL/F
- Part 2 (repeated once weekly [QW] dose, as data permits:
  - Day 1 (Cohort 6): $AUC_{(0-168)}$, C_{max}, C_{168}, t_{max}, t_{lag}
  - Day 8 (Cohort 6): $AUC_{(0-168)}$, C_{max}, C_{168}, t_{max}
  - Day 15 (Cohort 6): $AUC_{(0-t)}$, C_{max}, Cτ, t_{max}, $t_{1/2}$, and CL/F

- Part 3 (single dose): $AUC_{(0-24)}$, $AUC_{(0-inf)}$, C_{max}, C_{24}, t_{max}, t_{lag}, $t_{1/2}$, C_{last}, t_{last}, CL/F

Additionally, in Part 3 the parameters used for the treatment comparison of relative bioavailability of the single dose PiB formulation relative to the single dose tablet formulation, and the food effect of the tablet fed relative to tablet fasted state will be AUC(0-24), AUC(0-inf), and C_{max}.

8.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

Missing data will not be imputed, regardless of the reason.

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.5.1. Statistical Methodology Specification

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

8.1.5.1.1. Dose Proportionality (Power Model)

Part 1 and 2

In Part 1 where participants may participate in multiple cohorts the power model will be used to estimate the dose proportionality constant as follows:

$$y_{ij} = \theta_1 + \theta_2\, d_{ij} + s_i + \epsilon_{ij}$$

Where y_{ij} is log-PK of i-th participant to j-th dose, d_{ij} is j-th log-dose administered to i-th participant. θ_1 and θ_2 are population intercept and slope, respectively, s_i is random effect of i -th participant and ϵ_{ij} is random error of i -th participant in j-th dose.

The posterior distribution of the mean value μ_{ij} of the log-PK parameter is then described as:

$$\mu_{ij} \sim N(y_{ij}, \sigma^2)$$

In Part 2 where participants will only participate in one cohort and intra-participant variability cannot be estimated the following power model will be used to estimate the dose proportionality constant.

$$y_i = \theta_1 + \theta_2\, d_i + \epsilon_i$$

[2]

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

The posterior distribution of the mean value μ_i of the log-PK parameter is then described as:

$$\mu_i \sim N(y_i, \sigma^2)$$

In both models θ_2 represents the dose proportionality constant. The point estimate and 95% credible interval for this parameter will be estimated and reported using separate models for Part 1 and Part 2.

Non-informative prior distributions for the estimated parameters are defined below:

$$\theta_1 \sim N(0,10^2)$$

$$\theta_2 \sim N(0,10^2)$$

$$s_i \sim N(0, \tau_i)$$

$$\tau_i \sim Gamma(0.01,0.01)$$

$$\sigma^2 \sim Gamma(0.01,0.01)$$

8.1.5.1.2. Accumulation Ratio

Part 1

Predidicted daily dose accumulation from single dose data (Part 1) for AUC will be as follows:

$$Rp(AUC) = \frac{AUC(0-\infty)}{AUC(0-24)}$$

Point estimates of the mean ratio and associated 90% confidence intervals will be displayed by treatment.

Part 2

Accumulation will also be evaluated for each treatment by determining the ratio of Day 14 (Part 2 cohort 3 and 4) or Day 18 (Part 2 cohort 5) to Day 1 AUC(0-τ) (R(AUC(0-τ)), Cmax (R(Cmax)), and Cτ (R(Cτ)). Day 1 Cτ will be defined as the 24-hr post day 1 dosing concentration (C24 for Day 1). For part 2 cohort 3,4, and 5 the dosing interval is 24-hrs. Therefore, τ=24hrs.

For Cohort 6 accumulation will be evaluated by determining the ratio of third dose (occurring on Day 15) to first dose (Day 1) for AUC(0-τ) (R(AUC(0-τ)), Cmax

(R(Cmax)), and Cτ (R(Cτ)). For part 2 cohort 6 the dosing interval is 7 days (168 hrs). Therefore, τ=168 hrs. In Cohort 6, since sampling at 168 hrs post 3rd dose was not collected, it will be predicted using linear model based on the other collected timepoints post dose.

Point estimates of the mean ratios and associated 90% confidence intervals will be displayed by treatment.

Endpoint / Variables

- Rp(AUC) for Part 1
  Where
  $$Rp(AUC) = \frac{AUC(0-\infty)}{AUC(0-24)}$$
- R(AUC(0-τ)), R(Cmax), R(Cτ) on Days 1 and 14 for Part 2 Cohort 3 and 4 where, τ=24 hrs
- R(AUC(0-τ)), R(Cmax), R(Cτ) on Days 1 and 18 for Part 2 Cohort 5 where, τ=24 hrs
- R(AUC(0-τ)), R(Cmax), R(Cτ) on Days 1 and 15 for Part 2 Cohort 6 where, τ=168 hrs

Where
$$R(Parameter) = \frac{(Parameter\ Value\ \ on\ Day\ XX)}{(Parameter\ Value\ \ on\ Day\ 1)}$$

Model Specification

- In Part 1 the mean of the raw mean of the ratio of AUC(0-inf) to AUC(0-24) will be reported. There is no formal modeling.
- In the model for Part 2 Cohort 3,4,5,6 the ratio of the specific parameter will be the dependent variable, day will be included as a fixed effect categorical variable with the reference as Day 1, and participant will be included as a random effect.

Model Checking & Diagnostics

- A compound symmetry covariance structure for the R matrix will be used by specifying "type=CS" on the RANDOM line
- In the event that this model fails to converge, alternative correlation structures may be considered such as CSH.
- 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.
- Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Model Results Presentation
• For Part 1, point estimates of the means of AUC(0-inf) and AUC(0-24), the point estimate of the predicted accumulation ratio, and the associated 90% confidence interval will be presented in tabular format by treatment group. • For Part 2, point estimates of the Geometric least squares means and 90% confidence intervals for the accumulation ratio will be presented in tabular format by treatment group.
Subgroup Analyses
• Not Applicable.
Sensitivity and Supportive Analyses
• Not Applicable.

8.1.5.1.3. Assessment of Steady State

For Part 2 cohorts 3 and 4, steady-state VH3739937 concentrations will be assessed by estimating the slope of concentrations on pre-dose assessments on Days 2-14 (Part 2 cohort 3 and 4) and the day 15 24-hr post-dose (relative to dosing on day 14). For Part 2 cohort 5, steady state VH37339937 concentrations will be assessed by estimating the slop eof the concentrations of pre-dose assessments on Days 2-18 and the day 19 24-hr post-dose (relative to dosing on day 18).

To determine when steady state is achieved the separate mixed effects linear regression models will be estimated for each treatment and each subset of days. The first subset of days will include all $C\tau$ values for days 2-15. Then the value from the earliest timepoint will dropped and the analysis re-run. Earlier days will be iteratively dropped (e.g. Days 2-15, then Days 3-15, then Days 4-15, etc.) until only 3 dosing days, and the 24-hr post final dose assessment, remain. The final assessment of the slope will be determined by at least the last 3 pre-dose concentrations and the concentration 24 hours post last dose.

Endpoint / Variables
• $C\tau$ Day (2-15) for Part 2 Cohort 3 and 4 • $C\tau$ Day (2-19) for Part 2 Cohort 5
Model Specification
• In the model for Part 2 Cohort 3 and 4, $C\tau$ Day (2-15) will be the dependent variable, day will be included as a fixed effect, and participant will be included as a random effect • In the model for Part 2 Cohort 5, $C\tau$ Day (2-19) will be the dependent variable, day will be included as a fixed effect, and participant will be included as a random effect
Model Checking & Diagnostics
• Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption

of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Model Results Presentation
• Point estimates and 90% confidence intervals for the slope will be presented in tabular format by treatment group. The analysis will be conducted for all days (2-15 for Cohort 3 and 4 and 2-19 for Cohort 5) and repeated by dropping one earlier day at a time until the final 3 days of dosing remain (that is days 12-14 and day 15 for cohort 3 and 4 and days 16-18 and day 19 for cohort 5) . • Individual values of $C\tau$ Day (2-15) for Part 2 Cohort 3 and 4 will be plotted graphically by treatment group • Individual values of $C\tau$ Day (2-19) for Part 2 Cohort 5 will be plotted graphically by treatment group
Subgroup Analyses
• Not Applicable.
Sensitivity and Supportive Analyses
• Not Applicable.

8.1.5.1.4. Relative Bioavailability and Food Effect

Part 3

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

Endpoint / Variables
• Log-transformed AUC(0-24), AUC(0-inf) (or AUC(0-tlast) if AUC(0-∞) cannot be derived), and Cmax
Model Specification
• AUC(0-24), AUC(0-inf) and Cmax will be separately analysed using a mixed effects models. In each model the dependent variable will be the log-transformed PK parameter of interest (AUC(0-inf) or Cmax). • For the RBA model the primary comparison will be Tablet vs. PiB (B vs. A), the independent variables will include a fixed effect for treatment (PiB or Tablet) and period, and a random effect for participant. • For the Food effect model the primary comparison will be Tablet Fed vs. Tablet Fasted (B vs. C), the independent variables will include a fixed effect for fasting status (fed vs. fasted) and period, and a random effect for participant $\log(Pk\ Parameter) = \beta_0 + \beta_1 \text{Treatment} + \beta_2 Period + \gamma_i Subject$

Model Checking & Diagnostics
• A compound symmetry covariance structure for the R matrix will be used by specifying "type=CS" on the RANDOM line • In the event that this model fails to converge, alternative correlation structures may be considered such as CSH. • 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. • Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Model Results Presentation
• The estimated difference and CI obtained on the log scale will be exponentiated to provide an estimate of the fed to fasted or tablet to PiB ratio and its associated 90% CI. Estimates of within-subject variability (%CVw) will also be provided (%CVw=SQRT(exp(MSE) – 1)×100). %CVw represents a pooled measure of within-subject variability across all treatments. • Comparative plots of individual PK parameters will be generated by treatment on linear and semi-logarithmic scales. • Plots of adjusted geometric mean ratio of test to reference treatment together with 90% confidence intervals will be produced. • Listing of individual PK parameter ratios will be generated. • Supportive SAS output from statistical analysis will be generated.
Subgroup Analyses
• Not Applicable.
Sensitivity and Supportive Analyses
• Not Applicable.

8.2. Exploratory Pharmacokinetic Analyses

Exploratory analyses to assess the exposure response relationship between VH3739937 and QTcF following single and repeated administration (Part 1 & 2) will be conducted. Linear regression models using exposure as the independent variable and change from baseline in QTcF as the outcome variable will be run separately for Part 1 and 2.

$$y_{\delta QTcF} = \beta_0 + \beta_1 X_{Concentration}$$

The model estimates $\hat{\beta}_0$ and $\hat{\beta}_1$ and their 95% confidence intervals will be reported, and the regression line will be overlayed on the plot of the comparison of change in QTcF and concentration.

9. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The population PK analysis and pharmacodynamic analyses are exploratory endpoints that will be performed under a separate RAP and reported separately from the main clinical study report (CSR).

10. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Any exploratory pharmacokinetic/pharmacodynamic analyses only consider exploratory endpoints and will be analyzed and reported separately.

11. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

11.1. Study Population

11.1.1. Subject Disposition

The 'Summary of Subject Status and Subject Disposition for the Study Conclusion Record' and the 'Summary of Treatment Status and Reasons for Discontinuation of Study Treatment' will be repeated, with the reason for withdrawal/discontinuation categorized as due to the COVID-19 pandemic, or non-due to the COVID-19 pandemic based on information collected on the COVID-19 Pandemic Study Impact form. The summaries will be based on GSK Core Data Standards, and details are provided in Appendix 10.

11.1.2. Protocol Deviations

In addition to the overall summary of important protocol deviations, separate summaries will be produced of important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19. A listing of non-important protocol deviations related to COVID-19 will also be produced.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be listed by subject. The summaries will be based on GSK Core Data Standards, and details are provided in Appendix 10

11.1.3. Additional Displays for Participants with a COVID-19 Infection

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is "Confirmed", "Probable" or "Suspected" to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF.

A listing of the participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10

11.2. Safety

11.2.1. Assessment of COVID-19 AEs

A Standardised MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The incidence of AEs and SAEs (Fatal and Non-Fatal) of COVID-19, COVID-19 AEs leading to study drug discontinuation, and COVID-19 AEs leading to study withdrawal, and COVID-19 AEs by severity, will be obtained from standard AE and SAE summaries.

11.2.2. Impact of COVID-19 Pandemic on Safety Results

Since this single-site, United States-based, study began enrolment after the COVID-19 pandemic began, the beginning of pandemic measures in the United States had no effect on the safety results. Therefore, separate AE summaries and listings before and after the pandemic start are not produced.

12. REFERENCES

GlaxoSmithKline Document Number 2019N400726_01: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3739937 in Healthy Participants. Effective Date: 11-June-2020

Whitehead J. et al., Easy-to-implement Bayesian methods for dose-escalation studies in healthy participants, Biostatistics, 2, 47cs, 2, 47v 2001

13. APPENDICES

13.1. Appendix 1: Exclusions from Analysis Populations

Any analysis population exclusions, due to protocol deviations, will be discussed by the study team and documented.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Please refer to Protocol Section 1.2.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

All acceptable assessment windows are defined in Section 4.1 (dosing), Section 8.1.4 (ECG), of the protocol and the study reference manual. No assessment windows are redefined in the RAP.

13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

13.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to treatment administration(s).

Study Phase	Definition
Pre-Treatment	Date <Study Treatment Start Date
On-Treatment	Study Treatment Start Date≤ Date ≤ Study Treatment Stop Date + 22 days
Post-Treatment	Date > Study Treatment Stop Date + 22 days

13.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. (plus washout or protocol-specified time limit (e.g. half-life of drug, certain number of days, etc.). • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ 22 days]. • For studies with greater than one treatment period (e.g., crossover study) and the dates of changes in grade are collected, if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date [+ 22 days].

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.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software 9.4 or higher will be used.	
Reporting Area	
HARP Server	:\\us1salx00259.corpnet2.com
HARP Compound	:\arwork\gsk3739937\mid212548\final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1].	
Generation of RTF Files	
• RTF files will be generated for Tables, one RTF file per item. Listings will be generated in L10 format, and Figures will be generated in PDF format.	
Generation of xlm Files	
• xlm files will not be generated for the current reporting efforts	
Dictionaries	
• The current dictionary version in effect at the time of reporting will be used Adverse Events MedDRA 24.0 • Concomitant Medications GSKDRUG v 1.9 and WHODrug GLOBAL C3 March 1, 2020	

13.5.2. Reporting Standards

General
• The current GSK Statistical Display Standards in the GSK Standards Library (IDSL) will be applied for reporting, unless otherwise stated (Library Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): • Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings
Formats
• GSK Statistical Display 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 GSK Standard Statistical Display 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 GSK Standard Statistical Display Principle 5.05.1).

• Unscheduled or unplanned readings will be presented within the participant's listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to GSK Standard Statistical Display Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to GSK Standard Statistical Display Principals 7.01 to 7.13.

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to Standards for the Transfer and Reporting of PK Data document. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to the GSK Standard PK Display Standard. Refer to the GSK Standard Statistical Display Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: • Relative bioavailability (Treatment B / Treatment A) of AUC(0-24), AUC(0-inf), and Cmax • Food Effect (Treatment B / Treatment C) of AUC(0-24), AUC(0-inf), and Cmax • Predicted Dose accumulation of AUC single dose AUC $$Rp = \frac{AUC(0-\infty)}{AUC(0-24)}$$
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to GSK Standard PK Display Standard.
Untransformed PK parameter	tmax (TMAX), tlast (TLST), tlag (TLAG).
PK parameter listed only	lambda_z (LAMZ), lambda_z_lower (LAMZL), lambda_x_upper (LAMZU), No_points_lambda_z (LAMZNPT).

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Analysis 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. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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 First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

13.6.2. Study Population

Treatment Compliance
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** • Participants 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.

13.6.3. Safety

Adverse Events
AEs of Special Interest

• While VH3739937 does not have a defined list of AESI, the AESI for the similar compound GSK3640254 will be used for this study (apart from "HIV-1 resistance to GSK3640254" which is not applicable to this study of healthy volunteers). Details of specific SOCs and SMQs for AESI of GS3640254 are maintained by that compound's SRT. The list broadly includes the following items:
  ○ QT prolongation
  ○ GI intolerability/toxicity
  ○ Psychiatric events
  ▪ Suicidal ideation/behaviour
  ▪ Depression
  ▪ Bipolar disorder Psychosis
  ▪ Anxiety
  ▪ Sleep disorders
  ○ Nervous system disorders

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 : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

13.6.4. Pharmacokinetic

Derived pharmacokinetic data is described in Section 8.1.1.2. Additionally, daily dose accumulation from single dose data (Part 1) for AUC will be predicted as follows:

$$Rp = \frac{AUC(0-\infty)}{AUC(0-24)}$$

13.6.5. Pharmacodynamic

No pharmacodynamic endpoints will be derived or transformed.

13.6.6. Laboratory

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

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion was defined as complete if he/she has completed all phases of the study including the last visit and the last scheduled procedure shown in the schedule of activities • Withdrawn participants may be replaced in the study depending on study part and whether adequate sample size for a cohort as already been reached. • All available data from participants 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.

13.7.2. 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 participant 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 13.4.1) or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions: Missing start day: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: ○ If month and year of start date = month and year of study treatment start date then

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
o Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
o If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
o Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
• Completely missing start or end dates will remain missing, with no imputation applied.
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
o If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
o Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
o If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
• The recorded partial date will be displayed in listings.
</td></tr>
</table>

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Element	Reporting Detail
Laboratory Values and Adverse Events	• The Division of AIDS (DAIDS) grading for severity of laboratory toxicities and clinical adverse events, version 2.1, July 2017 will be used to assign grades to laboratory values. • When deriving the Grading for severity of laboratory toxicity only numeric criteria are considered. The following note will be included in the listing including laboratory severity output: "Grades were derived based on numeric criteria as defined in DAIDS Version 2.1 and did not take into consideration of clinical signs or symptoms which is needed for the final grade associated with the adverse event." • Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

13.8.2. Urinalysis Values

A participant is considered to have urinalysis results of PCI, if there is an increase in Protein or an increase in Occult Blood results during the study, or if microscopy is performed.

13.8.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	< 320	> 450
Absolute PR Interval	msec	< 120	> 200
Absolute QRS Interval	msec	< 75	> 110
Heart Rate	bpm	< 40	> 110
Change from Baseline			
Increase from Baseline QTcF	msec		>60

13.8.4. 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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range	
		Decrease	Increase
Systolic Blood Pressure	mmHg	≥ 40	≥ 40
Diastolic Blood Pressure	mmHg	≥ 20	≥ 20
Heart Rate	bpm	≥ 30	≥ 30

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
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)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library (GSK Standards Library)
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
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
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

13.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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[WinNonlin]

13.10. Appendix 10: List of Data Displays

All data displays will use the term "subject" rather than "participant" in accordance with CDSIC and GSK Statistical Display Standards.

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.44	NA
Safety	3.1 to 3.35	NA
Pharmacokinetic	4.1 to 4.10	4.1 to 4.20
Section	**Listings**	
ICH Listings	1 to 16	
Other Listings	17 to 34	

13.10.2. Mock Example Shell Referencing

Nonstandard specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic (PK)	PK_F1	PK_T1 PK_T2 PK_T3 PK_T4 PK_T5	NA
Safety	NA	NA	SAFE_L1

13.10.3. Deliverables

Delivery [Priority] [1]	Description
HL	Headline Data Delivery
SAC [1]	Final Statistical Analysis Complete

NOTES:

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

13.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record – Part 1	ICH E3, FDAAA, EudraCT	SAC [1], HL
1.2.	Safety	ES1	Summary of Subject Status and Subject Disposition for the Study Conclusion Record – Part 2	ICH E3, FDAAA, EudraCT	SAC [1], HL
1.3.	Safety	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record – Part 3	ICH E3, FDAAA, EudraCT	SAC [1], HL
1.4.	Safety	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record Related to COVID-19 Pandemic – Part 1	ICH E3, FDAAA, EudraCT	SAC [1]
1.5.	Safety	ES1	Summary of Subject Status and Subject Disposition for the Study Conclusion Record Related to COVID-19 Pandemic – Part 2	ICH E3, FDAAA, EudraCT	SAC [1]
1.6.	Safety	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record Related to COVID-19 Pandemic – Part 3	ICH E3, FDAAA, EudraCT	SAC [1]
1.7.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment– Part 1	ICH E3, Treatment group column will indicate treatment sequence to which the subject was assigned. Add Footnote: Since Part 1 only has a single dose per period, a participant's treatment status is complete if they take any dose within any period.	SAC [1]

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – Part 2	ICH E3, Treatment group column will indicate the treatment that the subject was taking at the time of discontinuation	SAC [1]
1.9.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – Part 3	ICH E3, Treatment group column will indicate the treatment that the subject was taking at the time of discontinuation Add Footnote: Since Part 3 only has a single dose per period, a participant's treatment status is complete if they take any dose within any period.	SAC [1]
1.10.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment Related to COVID-19 Pandemic– Part 1	ICH E3, Treatment group column will indicate the treatment that the subject was taking at the time of discontinuation Add Footnote: Since Part 1 only has a single dose per period, a participant's treatment status is complete if they take any dose within any period.	SAC [1]
1.11.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment Related to COVID-19 Pandemic – Part 2	ICH E3, Treatment group column will indicate the treatment that the subject was taking at the time of discontinuation	SAC [1]

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.12.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment Related to COVID-19 Pandemic – Part 3	ICH E3, Treatment group column will indicate the treatment that the subject was taking at the time of discontinuation Add Footnote: Since Part 3 only has a single dose per period, a participant's treatment status is complete if they take any dose within any period.	SAC [1]
1.13.	Safety	ES4	Summary of Subject Disposition at Each Study Period– Part 1	ICH E3	SAC [1]
1.14.	Safety	ES4	Summary of Subject Disposition at Each Study Period– Part 2	ICH E3	SAC [1]
1.15.	Safety	ES4	Summary of Subject Disposition at Each Study Period– Part 3	ICH E3	SAC [1]
1.16.	Safety	ES5	Summary of Reason for Withdrawal at Each Period – Part 1	FDAAA, EudraCT	SAC [1]
1.17.	Safety	ES5	Summary of Reason for Withdrawal at Each Period – Part 2	FDAAA, EudraCT	SAC [1]
1.18.	Safety	ES5	Summary of Reason for Withdrawal at Each Period – Part 3	FDAAA, EudraCT	SAC [1]
1.19.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements.	SAC [1]
1.20.	Safety	ES11	Summary of Outcome of Adverse Events Which Led to Study Withdrawal at Each Study Period – Part 1	EudraCT	SAC [1]
1.21.	Safety	ES11	Summary of Outcome of Adverse Events Which Led to Study Withdrawal at Each Study Period – Part 2	EudraCT	SAC [1]

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.22.	Safety	ES11	Summary of Outcome of Adverse Events Which Led to Study Withdrawal at Each Study Period – Part 3	EudraCT	SAC [1]
1.23.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID – Part 1	EudraCT/Clinical Operations	SAC [1]
1.24.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID – Part 2	EudraCT/Clinical Operations	SAC [1]
1.25.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID – Part 3	EudraCT/Clinical Operations	SAC [1]
1.26.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID Relative to COVID-19 Pandemic Measures – Part 1		SAC [1]
1.27.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID Relative to COVID-19 Pandemic Measures – Part 2		SAC [1]
1.28.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID Relative to COVID-19 Pandemic Measures – Part 3		SAC [1]
Protocol Deviation					
1.29.	Safety	DV1	Summary of Important Protocol Deviations – Part 1	ICH E3	SAC [1]
1.30.	Safety	DV1	Summary of Important Protocol Deviations – Part 2	ICH E3	SAC [1]
1.31.	Safety	DV1	Summary of Important Protocol Deviations – Part 3	ICH E3	SAC [1]
1.32.	Safety	DV1	Summary of Important Protocol Deviations and Relation with COVID-19 -Part 1	ICH E3	SAC [1]
1.33.	Safety	DV1	Summary of Important Protocol Deviations and Relation with COVID-19 -Part 2	ICH E3	SAC [1]
1.34.	Safety	DV1	Summary of Important Protocol Deviations and Relation with COVID-19 -Part 3	ICH E3	SAC [1]

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.35.	Screened	SP1	Summary of Study Populations	GSK Statistical Display Standard.	SAC [1]
Demographic and Baseline Characteristics					
1.36.	Safety	DM1xo	Summary of Demographic Characteristics – Part 1	ICH E3, FDAAA, EudraCT	SAC [1]
1.37.	Safety	DM1	Summary of Demographic Characteristics – Part 2	ICH E3, FDAAA, EudraCT	SAC [1]
1.38.	Safety	DM1xo	Summary of Demographic Characteristics – Part 3	ICH E3, FDAAA, EudraCT	SAC [1]
1.39.	Enrolled	DM11xo	Summary of Age Ranges – Part 1	EudraCT	SAC [1]
1.40.	Enrolled	DM11	Summary of Age Ranges – Part 2	EudraCT	SAC [1]
1.41.	Enrolled	DM11xo	Summary of Age Ranges – Part 3	EudraCT	SAC [1]
1.42.	Safety	DM6xo	Summary of Race and Racial Combination Details – Part 1	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
1.43.	Safety	DM6	Summary of Race and Racial Combination Details – Part 2	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
1.44.	Safety	DM6xo	Summary of Race and Racial Combination Details – Part 3	ICH E3, FDA, FDAAA, EudraCT	SAC [1]

13.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 1	ICH E3	SAC [1], HL

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.2.	Safety	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 2	ICH E3	SAC [1], HL
3.3.	Safety	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 3	ICH E3	SAC [1], HL
3.4.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – Part 1	ICH E	SAC [1]
3.5.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – Part 2	ICH E	SAC [1]
3.6.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – Part 3	ICH E	SAC [1]
3.7.	Safety	AE5B	Summary of All Drug-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 1	ICH E3	SAC [1], HL
3.8.	Safety	AE5B	Summary of All Drug-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 2	ICH E3	SAC [1], HL
3.9.	Safety	AE5B	Summary of All Drug-Related Adverse Events by Maximum Grade by System Organ Class and Preferred Term – Part 3	ICH E3	SAC [1], HL
3.10.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 1	FDAAA, EudraCT	IA [1], SAC [1]

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 2	FDAAA, EudraCT	IA [1], SAC [1]
3.12.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 3	FDAAA, EudraCT	IA [1], SAC [1]
3.13.	Safety	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by System Organ Class and Preferred Term – Part 1	Use GSK3640254 SRT spreadsheet at time of reporting to identify AESI	SAC [1]

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	Safety	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by System Organ Class and Preferred Term – Part 2	Use GSK3640254 SRT spreadsheet at time of reporting to identify AESI	SAC [1]
3.15.	Safety	AE5B	Summary of Adverse Events of Special Interest by Maximum Grade by System Organ Class and Preferred Term – Part 3	Use GSK3640254 SRT spreadsheet at time of reporting to identify AESI	SAC [1]
Serious and Other Significant Adverse Events					
3.16.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 1	FDAAA, EudraCT	SAC [1], HL
3.17.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 2	FDAAA, EudraCT	SAC [1], HL
3.18.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part 3	FDAAA, EudraCT	SAC [1], HL

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term – Part 1	GSK Statistical Display Standard	SAC [1], HL
3.20.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term – Part 2	GSK Statistical Display Standard	SAC [1], HL
3.21.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term – Part 3	GSK Statistical Display Standard	SAC [1], HL
Laboratory: Chemistry					
3.22.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3, Page by Part	SAC [1] ,HL
3.23.	Safety	LB15A	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC [1]
Laboratory: Hematology					
3.24.	Safety	LB1	Summary of Haematology Changes from Baseline	ICH E3, Page by Part	SAC [1] ,HL
3.25.	Safety	LB15A	Summary of Worst Case Haematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3, Page by Part	SAC [1]
Laboratory: Urinalysis					
3.26.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline – Part 1	ICH E3,For discrete or character values only	SAC [1], HL
3.27.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline – Part 2	ICH E3,For discrete or character values only	SAC [1], HL

Safety: Tables					
No.	**Population**	**GSK Standard/ Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.28.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline – Part 3	ICH E3,For discrete or character values only	SAC [1], HL
ECG					
3.29.	Safety	EG1	Summary of ECG Findings - Part 1	GSK Statistical Display Standard	SAC [1]
3.30.	Safety	EG1	Summary of ECG Findings – Part 2	GSK Statistical Display Standard	SAC [1]
3.31.	Safety	EG1	Summary of ECG Findings – Part 3	GSK Statistical Display Standard	SAC [1]
3.32.	Safety	EG10A	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	GSK Statistical Display Standard, ICH E14, page by part	SAC [1], HL
3.33.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	GSK Statistical Display Standard, page by part	SAC [1]
3.34.	Safety	EG11A	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	GSK Statistical Display Standard, page by part	SAC [1], HL
Vital Signs					
3.35.	Safety	VS3A	Summary of Vital Sign Shifts from Baseline Relative to Potential Clinical Importance (PCI) Criteria	GSK Statistical Display Standard, page by part	SAC [1], HL

13.10.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PK01	Summary of VH3739937 Plasma Pharmacokinetic Concentration (ng/mL) -Time Data by Treatment	Page by part	SAC [1]
4.2.	PK	PK03	Summary of Derived VH3739937 Plasma Pharmacokinetic Parameters by Treatment		SAC [1],HL
4.3.	PK	PK05	Summary of Log-Transformed Derived VH3739937 Plasma PK Parameters by Treatment		SAC [1] ,HL
Dose Proportionality, Accumulation, and Steady State					
4.4.	PK	PK_T1	Summary Results of Single Dose Proportionality Assessment Using Power Model – Part 1	Stats output, Non-Standard Shell PK_T1 PK parameters: AUC(0-inf), AUC(0-t), Cmax	SAC
4.5.	PK	PK_T1	Summary Results of Multiple Dose Proportionality Assessment Using Power Model – Part 2	Stats output Non-standard shell PK_T1 PK parameters: AUC(0-inf), AUC(0- τ), Cmax	SAC
4.6.	PK	PK_T2	Summary Results of Steady State VH3739937 Concentrations Assessment – Part 2	Stats output Non-standard shell PK_T2 Use up to day 14 for cohort 3 and 4 and day 18 for cohort 5.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				Add footnote: Ctrough was collected on days 2,3,4,6,8, 10,11,12,13,14,15 for cohort 3 and 4 and days 2,3,4,6,8, 10,11,12,13,14,15, 16, 17,18 for cohort 5. Use C_τ to determine steady state for daily dosing MAD. See example from Table 4.13 from study 207187	
4.7.	PK	PK_T3	Summary Results of VH3739937 PK Parameter Treatment Comparisons Predicted Accumulation Ratio- Part 1	Stats output, Non-Standard Shell at end of RAP Non-standard shell PK_T3	SAC
4.8.	PK	PK_T4	Summary Results of VH3739937 PK Parameter Treatment Comparisons Accumulation Ratio- Part 2	Stats output, Non-standard shell PK_T4 Add footnote: In Cohort 6, since sampling at 168 hrs (7 days) post 3rd dose was not collected, it will be approximated by 192 hrs post dose.	SAC
Relative Bioavailability/Food Effect					
4.9.	PK	PK_T5	Summary of Result of Plasma VH3739937 Pharmacokinetic Parameter Treatment Comparisons for Relative Bioavailability	Stats output	SAC [1], HL

Pharmacokinetic: Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				PK Parameters: $AUC_{(0-24)}$, $AUC_{(0-inf)}$, and C_{max} Ratio: Test/Reference (Tablet/PiB) See study mid208131 Table 4.4 for reference Non-standard shell PK_T5	
4.10.	PK	PK_T5	Summary of Result of Plasma VH3739937 Pharmacokinetic Parameter Treatment Comparisons for Food Effect	Stats output PK Parameters: $AUC_{(0-24)}$, $AUC_{(0-inf)}$, and C_{max} Ratio: Test/Reference (Fed Tablet/Fasted Tablet). See study mid208131 Table 4.4 for reference Non-standard shell PK_T5	SAC [1], HL

13.10.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PK24	Individual VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	Paged by Dose, overlay all participants for each dose. Include LOQ line in plot. See Fig 4.1 from mid207187	SAC [1]
4.2.	PK	PK24	Individual VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 2	Paged by Dose and Day, overlay all participants for each dose. Include Day 1 and 14 for Cohort 3 and 4. Include Day 1, 14, and 18 for Cohort 5 See fig 4.6 from mid207187 Include LOQ line in plot.	SAC [1]
4.3.	PK	PK16B	Individual VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 3	Paged by participant, overlay all treatments for each participant. Include LOQ line in plot.	SAC [1]
4.4.	PK	PK17	Mean VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	By treatment. Use nominal times in X axis.	SAC [1]
4.5.	PK	PK17	Mean VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 2	By treatment. Use nominal times in X axis.	SAC [1]
4.6.	PK	PK17	Mean VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 3	By treatment. Use nominal times in X axis.	SAC [1]
4.7.	PK	PK18	Median VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 1	By treatment. Use nominal times in X axis.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.8.	PK	PK18	Median VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 2	By treatment. Use nominal times in X axis.	SAC [1]
4.9.	PK	PK18	Median VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 3	By treatment. Use nominal times in X axis.	SAC [1]
4.10.	PK	PK24	Individual VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Part 3	Paged by treatment, overlay all participants for each treatment. Show all timepoints. Include LOQ line in plot. See Fig 4.1 from mid207187	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.11.	PK	PK24	Plasma VH3739937 Trough Concentration-Time Plots (Linear and Semi-Log) by Cohort by Day - Part 2	All Subjects Overlay - Days 1 Through 14 for Cohort (3 and 4) Days 1-18 for Cohort 5. All points for Cohort 6 Trough Concentrations Only Add footnote: For Cohort 3 and 4 Pre-dose (trough) concentrations shown for days 1-14. Last dose taken on Day 14. Days 15-19 are follow-up visits. For Cohort 5: Pre-dose (trough) concentrations shown for days 1-18. Last dose taken on Day 18. Days 19-23 are follow-up visits. See fig 4.62 from mid207187	

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Relative Bioavailability/Food Effect					
4.12.	PK	PK28	Geometric Mean Treatment Ratio and 90% Confidence Interval of VH3739937 PK Parameters for Relative Bioavailability	Stats output: use mean from Table 4.12 See Reference Figure 4.4 from mid208131 PK Parameters: AUC $_{(0-24)}$, AUC$_{(0-inf)}$, and C_{max} Ratio: Test/Reference (Tablet/PiB)	SAC [1]
4.13.	PK	PK28	Geometric Mean Treatment Ratio and 90% Confidence Interval of VH3739937 PK Parameters for Food Effect	Stats output: use mean from Table 4.13 See Reference Figure 4.4 from mid208131 PK Parameters: AUC $_{(0-24)}$, AUC$_{(0-inf)}$, and C_{max} Ratio: Test/Reference (Tablet Fed/Tablet Fasted)	SAC [1]
4.14.	PK	PK25	Comparative Plot of Individual Plasma VH3739937 PK Parameters for Relative Bioavailability by Treatment (Linear and Semi-log)	PK Parameters: AUC $_{(0-24)}$, AUC$_{(0-inf)}$, and C_{max} Treatments and positioning: PiB Fed on left, Tablet Fed on right.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.15.	PK	PK25	Comparative Plot of Individual Plasma VH3739937 PK Parameters for Food Effect by Treatment (Linear and Semi-log)	PK Parameters: $AUC_{(0-24)}$, $AUC_{(0-inf)}$, and C_{max} Treatments and positioning: Tablet Fasted on left, Tablet Fed on Right side	SAC [1]
4.16.	PK	PK_F1	Scatter Plot of Individual QTcF Change from Baseline vs Time Matched VH3739937 PK Concentration – Part 1	Stats Output (for regression) Non-Standard Figure See shell at end of RAP, Reference study mid207187 Figure 5.1, Overlay regression line and 95% CI, print Beta regression line on plot.	SAC [1]
4.17.	PK	PK_F1	Scatter Plot of Individual QTcF Change from Baseline vs Time Matched VH3739937 PK Concentration – Part 2	Non-Standard Figure see shell at end of RAP, Reference study mid207187 Figure 5.2	SAC [1]
4.18.	PK	PK24	Individual VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Weekly Dosing Cohort 6	Include all timepoints, with time relative to first dose. Keep dots small or remove to reduce clutter. See Figure 4.6 from mid207187 Include LOQ line in plot.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.19.	PK	PK17	Mean VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Weekly Dosing Cohort 6	Include all timepoints, with time relative to first dose. Use nominal times in X axis.	SAC [1]
4.20.	PK	PK17	Median VH3739937 Plasma Concentration-Time Plots (Linear and Semi-log) – Weekly Dosing Cohort 6	Include all timepoints, with time relative to first dose. Use nominal times in X axis.	SAC [1]

13.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Safety	ES2xo	Listing of Reasons for Study Withdrawal	ICH E3	SAC [1]
2.	Safety	SD2xo	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [1]
3.	Safety	BL1xo	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC [1]
Protocol Deviations					
4.	Safety	DV2xo	Listing of Important Protocol Deviations	ICH E3	SAC [1]
5.	Safety	IE3xo	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [1]
Populations Analysed					
6.	Safety	SP3xo	Listing of Subjects Excluded from Any Population	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
7.	Safety	DM2xo	Listing of Demographic Characteristics	ICH E3	SAC [1]
8.	Safety	DM9xo	Listing of Race	ICH E3	SAC [1]
Exposure and Treatment Compliance					
9.	Safety	EX3xo	Listing of Exposure Data	ICH E3	SAC [1]
10.	Safety	SAFE_L1	Listing of Meal Data	Non-standard shell. Reference Study mid208131 Listing 12	SAC [1]
Adverse Events					

ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	Safety	AE8CPxo	Listing of All Adverse Events	ICH E3. Page by Part	SAC [1],HL
12.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3, Page by part	SAC [1]
Serious and Other Significant Adverse Events					
13.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3, Page by part	SAC [1]
14.	Safety	AECP8xo	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3, Page by Part	SAC [1]
All Laboratory					
15.	Safety	LB5Axo	Listing of All Laboratory Data for Subjects with Any Toxicity	ICH E3	SAC [1]
16.	Safety	UR2xo	Listing of All Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [1]

13.10.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
17.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC [1]
18.	Safety	TA1xo	Listing of Planned and Actual Treatments	GSK Statistical Display Standard	SAC [1]
19.	Enrolled	PAN5	Country Level Listing of Start Dates of COVID-19 Pandemic Measures		SAC [1]
Protocol Deviation					
20.	Safety	DV2xo	Listing of All Non-Important COVID-19 Related Protocol Deviations		SAC [1]
21.	Safety	PAN7	Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic		SAC [1]
Prior and Concomitant Medications and Medical History					
22.	Safety	CM10xo	Listing of Concomitant Medications	GSK Statistical Display Standard, page by part	SAC [1]
23.	Safety	MH2xo	Listing of Medical Conditions	Page by Part	SAC [1]
Adverse Events					
24.	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events		SAC [1]

Non-ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
25.	Safety	EG3xo	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC [1]
Vital Signs					
26.	Safety	VS4xo	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC [1]
Laboratory					
27.	Safety	LB14	Listing of Laboratory Data with Character Results		SAC [1]
CSSRS					
28.	Safety	CSSRS4	Listing of C-SSRS Suicidal Ideation and Behaviour Data	Include only subjects with at least one positive (Yes) response	SAC [1]
PK Endpoints					
29.	PK	PK07xo	Listing of VH3739937 Plasma Pharmacokinetic Concentration-Time Data Treatment		SAC [1]
30.	PK	PK13xo	Listing of Derived VH3739937 Plasma Pharmacokinetic Parameters by Treatment		SAC [1]
Hepatobiliary (Liver):					
31.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	GSK Hepatic Safety Panel	SAC [1]
32.	Safety	LIVER15	Liver Stopping Event Profile	GSK Hepatic Safety Panel	SAC [1]
33.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC [1]
34.	Safety	MH2xo	Listing of Medical Conditions for Subjects with Liver Stopping Events	Optional listing	SAC [1]

13.11. Appendix 11: Example Mock Shells for Data Displays

Data Displays available on Request