TITLE PAGE

Protocol Title: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3640254 in Healthy Participants

Protocol Number: 207187 / 04

Short Title: GSK3640254 FTIH study in healthy volunteers

Compound Number: GSK3640254

Sponsor Name and Legal Registered Address:

ViiV Healthcare UK Limited

980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information PPD DO, MPH;
PPD

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SPONSOR SIGNATORY:

PPD

PPD

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Date

PPD , DO, MPH
V evelopment
ViiV Healthcare

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 04	17-MAY-2018
Amendment 03	5-Dec-2017
Amendment 02	03-AUG-2017
Amendment 01	12-Jul-2017
Original Protocol	25-May-2017

Amendment 02; 03-Aug-2017

Overall Rationale for the Amendment: This amendment makes several notable changes to the protocol. First, details about the components of a full physical exam are described (including a neurologic exam); additionally, full physical exams now replace brief physical exams. Second, given the risk of neuropsychiatric events, a clinician (or qualified designee) administered Columbia Suicide Severity Rating Scale (CSSRS) has been incorporated into screening for all subjects (SAD and MAD); any subject with a positive (abnormal) response confirmed by the investigator will be excluded from participation. Additionally, the CSSRS has been incorporated into the on-treatment portion of the MAD only. Third, the emergence of any discontinuation criteria (including emergence of an SAE or emergence of any positive (abnormal) response confirmed by the investigator on the CSSRS during the on-treatment phase of the MAD) now requires discontinuation from the trial. More clarity is provided regarding the expected human effective dose range of GSK3640254 and the maximum single dose (200 mg if current assumptions are valid). Finally, the text regarding the 400 mg single dose in the event that exposures to GSK3640254 were lower than projected was removed.

Amendment 03; 05-Dec-2017

The primary purpose of this protocol amendment (03) is to increase the maximum dose in the SAD part of the study from 200 mg to ≤ 700 mg, in relation to human exposure to GSK3640254 being approximately 70% lower than predicted based on animal data. Preliminary PK parameters for GSK3640254 following single dose administration of 1, 3, and 10 mg show exposures that were lower along with a longer half-life than predicted based on animal data. The prediction for a 10 mg dose were a mean Cmax of 197 ng/mL, a mean AUC of 3430 ng.h/mL and a mean half-life of 15 hours. The observed Cmax was approximately 75% lower, the AUC was approximately 65% lower and the half-life was about 70% longer. Taking into consideration the actual human PK profile of GSK3640254 at 1, 3 and 10 mg, the minimally anticipated efficacious dose (X) has increased from 40 mg to 70 mg with an accumulation upon repeated once daily administration increasing from 50% to approximately 115%. In order to evaluate exposure anticipated at the maximum MAD dose of up to 4X, higher doses up to 9X will need to be evaluated in the SAD. Thus, this amendment is to enable the evaluation of the safety/tolerability and pharmacokinetics of single doses of GSK3640254 at doses ≤ 700 mg in healthy volunteers continuing to participate in Cohorts 1 and 2. Specifically, the

proposed higher doses will be evaluated in Period 4 (Cohort 1, ≤ 400 mg; Cohort 2, ≤ 700 mg). Other, non-major changes, have also been incorporated.

Amendment 04; 17-MAY-2018

The purpose of this protocol amendment (04) is to study a higher dose of 320 mg QD for 14 days in the MAD part of the study (see Cohort 6 in Figure 1). The MAD 320 mg QD dose would explore steady-state Cmax values greater than those explored in the SAD study (which is not permitted by the current version of the protocol). This dose of 320 mg QD is four times the projected minimum effective dose (~80 mg QD) and is in line with the MAD PK stopping Criteria in the current approved protocol (amendment 03/ 05 December 2017); specifically, the probability of any subject having an AUC > 61.1 µg/mL is 42% (data through May 9, 2018). A MAD dose of 320 mg QD allows for a thorough evaluation of PK/QT relationship and a greater safety margin in subsequent clinical trials in patients.

The totality of preliminary PK and safety/tolerability data to date shows the MAD 320 mg QD dose is clinically and scientifically reasonable (see Section 3.2.2 for full details). Specifically, GSK3640254 following single dose administration ultimately showed a plateauing of exposure at the 700 mg dose. On Day 14, the mean Cmax for the MAD 200 mg dose (1841 ng/ml in Cohort 5) approximated that seen in the SAD at 400 and 700 mg doses (1881 and 1761 ng/ml, respectively). Since the current protocol does not permit a dose in the MAD to surpass the Cmax studied in the SAD, the ViiV/ GSK Dose Escalation Committee opened the Expansion Cohort (currently ongoing) with a 200 mg dose (See Figure 1) at the conclusion of Cohort 5. Briefly, there have been no significant clinical safety/tolerability findings in the SAD or MAD through May 7, 2018. Preliminary ongoing data review show no deaths or SAEs. There have been 4 individual AEs leading to discontinuation. There have been 10 individual AEs related to blinded study medication. Preliminary review of blinded safety data for the: 1) SAD show 17 subjects experienced 60 individual AEs (58 Grade 1; Two Grade 2) and 2) MAD show 23 subjects experienced 79 individual AEs (77 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System and Gastrointestinal Disorders without a dose/AE relationship. Subjects recruited for the 320 mg QD Cohort will have the same inclusion/exclusion criteria, have the same study and subject stopping criteria, and undergo the same intensive safety evaluation as previously treated subjects in the MAD. Combined, based upon the preliminary safety and PK data gathered to date (see Section 3.2.2 for full details) subjects will be adequately monitored.

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 5.1 Overall Design	Figure 1 changed and MAD Expansion Cohort Dose added	The actual doses for all Cohorts and Periods updated for the SAD and MAD
Section 3.2.2 Preliminary Safety and PK data in Current Study	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 3.3 Benefit Risk Assessment	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting an unchanged benefit risk assessment for a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 5.1 Overall Design (Part 2 [MAD])	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 5.5.2 Predicted Human Effective Dose	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)
Throughout	Minor editorial and document formatting revisions	Minor, therefore not summarized

TABLE OF CONTENTS

PAGE

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3

1. SYNOPSIS 9

2. SCHEDULE OF ACTIVITIES (SOA) 13

3. INTRODUCTION 20
   - 3.1. Study Rationale 20
   - 3.2. Background 20
     - 3.2.1. Background Key Safety and PK data with a Prior Maturation Inhibitor (GSK3532795) 21
     - 3.2.2. Preliminary Safety and PK data in Current Study (SAD doses 1 - 700 mg and MAD doses 50 – 200 mg daily) 22
   - 3.3. Benefit/Risk Assessment 28
     - 3.3.1. Risk Assessment 30
     - 3.3.2. Benefit Assessment 32
     - 3.3.3. Overall Benefit:Risk Conclusion 32
     - 3.3.4. Acute Monitoring in FTIH Studies 32

4. OBJECTIVES AND ENDPOINTS 33

5. STUDY DESIGN 34
   - 5.1. Overall Design 34
   - 5.2. Number of Participants 37
   - 5.3. Participant and Study Completion 37
   - 5.4. Scientific Rationale for Study Design 37
   - 5.5. Dose Justification 38
     - 5.5.1. Predicted Human Pharmacokinetics 38
     - 5.5.2. Predicted Human Effective Dose 38
     - 5.5.3. Part 1 (SAD) Starting Dose and Dose Escalation 39
     - 5.5.4. Part 2 (MAD) Starting Dose and Dose Escalation 41
     - 5.5.5. Dose Escalation Committee 42
     - 5.5.6. Anticipated Exposure and Safety Cover for a Range of Potential Doses 42

6. STUDY POPULATION 44
   - 6.1. Inclusion Criteria 44
   - 6.2. Exclusion Criteria 45
   - 6.3. Lifestyle Restrictions 47
     - 6.3.1. Meals and Dietary Restrictions 47
     - 6.3.2. Drugs, Caffeine, Alcohol, and Tobacco 47
     - 6.3.3. Activity 48
   - 6.4. Screen Failures 48

7. TREATMENTS 49
   - 7.1. Treatments Administered 49
   - 7.2. Dose Modification 49
   - 7.3. Method of Treatment Assignment 49
   - 7.4. Blinding 50

7.5. Preparation/Handling/Storage/Accountability 50
7.6. Treatment Compliance 51
7.7. Concomitant Therapy 51
7.8. Treatment after the End of the Study 52

8. DISCONTINUATION CRITERIA 53
8.1. Discontinuation of Study Treatment 53
8.1.1. Liver Chemistry Stopping Criteria 53
8.1.2. QTc Stopping Criteria for Individual Participants 54
8.1.3. PK Stopping Criteria for SAD and MAD 54
8.1.4. Clinical criteria for Stopping the Study 54
8.1.5. Rechallenge 55
8.1.5.1. Study Treatment Restart or Rechallenge 55
8.2. Withdrawal from the Study 55
8.3. Lost to Follow Up 55

9. STUDY ASSESSMENTS AND PROCEDURES 57
9.1. Efficacy Assessments 57
9.2. Adverse Events 57
9.2.1. Time Period and Frequency for Collecting AE and SAE Information 58
9.2.2. Method of Detecting AEs and SAEs 58
9.2.3. Follow-up of AEs and SAEs 58
9.2.4. Regulatory Reporting Requirements for SAEs 58
9.2.5. Pregnancy 59
9.3. Treatment of Overdose 59
9.4. Safety Assessments 59
9.4.1. Physical Examinations 60
9.4.2. Vital Signs 60
9.4.3. Electrocardiograms 60
9.4.3.1. 12-lead safety ECGs 60
9.4.3.2. Cardiodynamic assessment (ECGs extracted from Holter recordings) 60
9.4.4. Clinical Safety Laboratory Assessments 62
9.4.5. Suicidal Risk Monitoring 63
9.4.6. GI Toxicity Evaluation and Monitoring Plan 63
9.5. Pharmacokinetics 66
9.6. Pharmacodynamics 66
9.7. Genetics 67

10. STATISTICAL CONSIDERATIONS 68
10.1. Sample Size Determination 68
10.2. Populations for Analyses 68
10.3. Statistical Analyses 69
10.3.1. Safety Analyses 69
10.3.2. Other Analyses 69
10.3.3. Interim Analyses 70
10.3.4. Final Analyses 72

11. REFERENCES 73

12. APPENDICES 75

12.1. Appendix 1: Abbreviations and Trademarks....75
12.2. Appendix 2: Clinical Laboratory Tests....78
12.3. Appendix 3: Study Governance Considerations....80
12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....84
12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information....89
12.6. Appendix 6: Genetics....92
12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments....93
12.8. Appendix 8: Protocol Amendment History....95

1. SYNOPSIS

Protocol Title: A Double-Blind (Sponsor Unblinded), Randomized, Placebo-Controlled, Single and Repeated Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK3640254 in Healthy Participants

Short Title: GSK3640254 FTIH study in healthy participants

Rationale: The inhibition of maturation and release of human immunodeficiency virus-1 (HIV-1) is a novel target for drug development, distinct from viral protease, reverse transcriptase and integrase. There are no maturation inhibitors (MI) approved for the treatment of HIV infection. GSK3640254 is a MI that displays *in vitro* evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development. The goal of this study is to gain information on the safety, tolerability, and pharmacokinetic properties of GSK3640254. This study will enable further clinical development of GSK3640254, including a Phase IIA Proof of Concept (PoC) study in HIV-infected patients.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To investigate the safety and tolerability of GSK3640254 following single and repeated daily administration	• GSK3640254 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
Secondary	
• To describe the PK of GSK3640254 following single and repeated daily administration	• GSK3640254 PK parameters: Part 1 (single dose): AUC(0-24), AUC(0-tlast), AUC(0-inf), Cmax, C24, tmax, tlag, t1/2, Clast, tlast, CL/F. Part 2 (Repeated QD doses for 14 days): Day 1: AUC(0-24), Cmax, C24, tmax, tlag Day 14: AUC(0-τ), Cmax, Cτ, tmax, t1/2, and CL/F
• To examine dose proportionality following single and repeated doses of GSK3640254 • To assess accumulation of GSK3640254	• GSK3640254 Single dose: AUC (0-inf), Cmax. Repeat dose AUC(0-τ), Cmax, Cτ • Accumulation ratios: R AUC(0-τ), R

Objective	Endpoint
• To assess time to steady-state of GSK3640254	(Cmax), R (Cτ) • Pre-dose concentrations on Day 2 -14 (Part 2)

ECG= Electrocardiogram; AUC(0-24) = Area under the plasma concentration time curve from zero to 24; AUC(0-inf) = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; Cmax= Maximum observed concentration; tmax= Time of occurrence of Cmax; t1/2= Apparent terminal phase half-life; CL/F= Apparent oral clearance

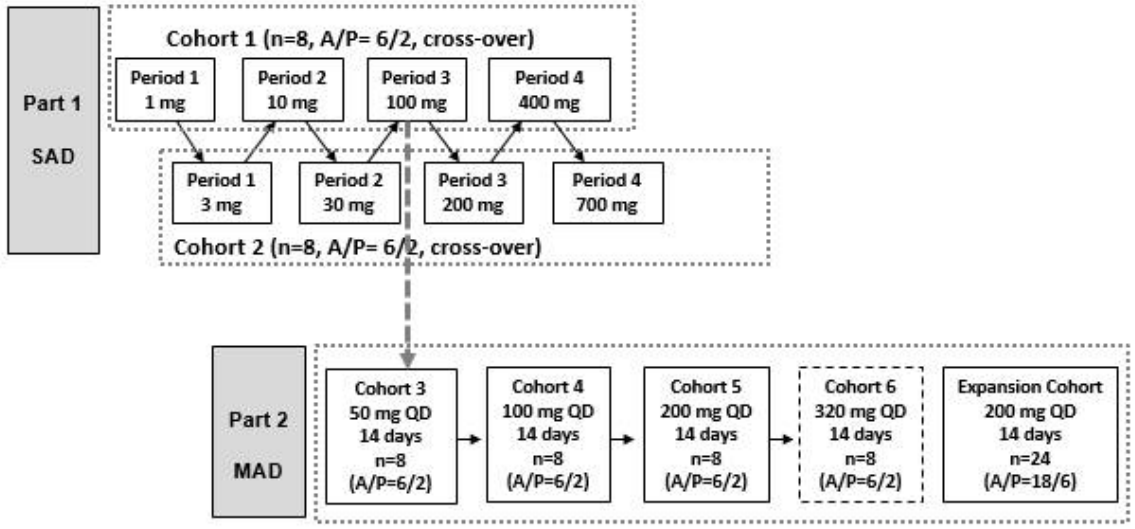
Overall Design:

This study is a Phase 1, double-blind (sponsor-unblinded), randomized, placebo-controlled, single- and repeat-dose escalation study of GSK3640254 in healthy participants.

A summary of the overall study design, including doses, sample size, and order, is presented in Figure 1; Schedule of Activities (**SoA**) tables are included in Section 2.

The proposed dosing schedule is designed to investigate single oral doses of GSK3640254 initially in Part 1 and then, at a suitable cross-over point (described below), repeated once-daily oral dosing of GSK3640254 in Part 2. All doses will be administered immediately following a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat), unless otherwise indicated.

Figure 1 Phase 1 Study in Healthy Participants using planned doses of GSK3640254



Note: A=active, P=placebo. The doses shown here were/are being completed. Amendment 04 proposes to evaluate a 320 mg Daily dose in MAD Cohort 6.

Number of Participants:

A total of approximately 72 randomized participants will be targeted for the entire study. Part 1 will randomize approximately 16 participants, 8 participants in each of Cohort 1 and Cohort 2. Part 2 will randomize approximately 56 participants, 8 participants in each of Cohorts 3 to 6 and 24 participants in the Expansion Cohort.

If participants prematurely discontinue the study in the single ascending dose (SAD), they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment sequence, starting where the prior participant prematurely discontinued. Previously administered doses will not be repeated by replacement subjects if dose escalation criteria are met.

If participants prematurely discontinue the study in the MAD, they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment in the same Cohort where the prior participant prematurely discontinued.

Treatment Groups and Duration:

Part 1 (SAD):

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts of eight healthy participants each. Each of these two cohorts will contain up to four escalating doses of GSK3640254; no more than 8 doses will be assessed in Part 1. The interlocking design as shown in the schematic in Figure 1 and the randomization sequence will allow the 8 participants in each Cohort to potentially receive one of the two lowest and one of the two highest doses of GSK3640254. In each escalating dose period, six participants will be randomized to GSK3640254 and two participants will be randomized to placebo. Each participant will receive placebo once.

To conservatively assess safety in the SAD, within each period and Cohort, 2 out of the 8 participants will serve as sentinel participants with one receiving GSK3640254 and the other receiving placebo (PBO or P in study design scheme). These sentinel participants will be followed clinically for 24 hours after dose administration to monitor the emergence of adverse events. Assuring that there are no safety concerns upon 24 hour review of safety data (e.g. vital signs, ECGs, and adverse events) by the Principal Investigator (PI) for the sentinel participants, the remaining 6 participants will subsequently be treated with either GSK3640254 or PBO according to randomization schedules.

Dose escalation in Part 1 will be determined by the ViiV Healthcare (VH)/ GlaxoSmithKline (GSK) study team and the PI based on the double-blind (sponsor-unblinded) safety data and the PK data from the previous dosing period(s). Dose escalation will not exceed approximately 3-fold between doses up to approximately the predicted minimally effective dose (see Section 5.5) and will not exceed 2-fold thereafter. Twenty-four hour post-dose safety and PK data from a minimum of 4 participants

receiving GSK3640254 are required for dose escalation. Dose escalation will be guided by safety as well as the SAD PK stopping criteria.

Continuous ECGs will be recorded on the day before dosing (Day -1), Day 1, and Day 2 for extraction of ECGs paired with PK sampling.

Part 2 (MAD):

Part 2 (MAD) consists of four ascending repeat-dose cohorts (Cohorts 3 to 6), each with 8 participants (active/PBO=6/2) who will receive a once-daily dose of GSK3640254 or PBO for 14 days. The earliest point at which Part 2 of the study will be conducted is once the single dose safety and preliminary PK data for the anticipated minimally effective dose have been evaluated in the SAD (see Figure 1, MAD). 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 previous dosing period(s). Specifically, 14 days of safety and PK data from a minimum of four participants receiving active drug will be required for dose escalation. In this part of the MAD study, continuous ECGs will be recorded on the day before the first dose (Day -1) and Days 1, 2, 14, and 15 for extraction of ECGs paired with PK sampling.

Part 2 also includes an Expansion Cohort to evaluate the rate of gastrointestinal (GI) intolerability in 24 participants (active/PBO =18/6). The expansion cohort was conducted once the evaluation of the safety and PK from Cohorts 3 – 5 were available. The dose chosen was 200 mg (see Figure 1, MAD).

Participants in both parts will have a screening visit within 28 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 12 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

SAD Cohorts 1 and 2 Screening

Procedure	Screening (up to 28 days before Day 1)
Outpatient Visit	X
Informed Consent	X
Inclusion/Exclusion Criteria and Demography	X
Medical/medication/ drug/alcohol history	X
Full Physical Exam[1]	X
Columbia Suicide Severity Rating Scale (CSSRS)	X
Height, Weight, BMI	X
Vital signs	X
12 Lead ECG	X
Screening Holter	X
Pregnancy Test	X
Drug/alcohol/cotinine screen	X
HbsAg, HCV, HIV tests	X
Hem/Chem/Urine tests	X

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

SAD Cohorts 1 and 2 On-Treatment: Before, During, and After Dosing in Each Period

Procedure	Periods 1 through 4																					Follow-up (7-14 days post last dosing)
	Day -2	Day -1	Day 1															Day 2	Day 3	Day 4	Day 5	
			Pre-dose	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	3.5 h	4 h	4.5 h	5 h	6 h	8 h	12 h	24 h	48 h	72 h	96 h	
Admission to Unit	X																					
Outpatient Visit																						X
Full Physical Exam[1]	X	X																	X			X
Weight, BMI[2]		X																				
Vital signs		X				X		X					X		X		X	X	X	X	X	X
12-lead safety ECGs	X	X	X			X		X				X			X		X	X	X	X	X	X
Continuous ECG (full time matched baseline on Day-1)[3]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy Test	X																					X[4]
Drug/alcohol/cotinine screen	X																					
Hem/Chem/Urine tests	X																	X	X		X	X
Fasting Lipid test	X																				X	X
Single Dosing with GSK3640254 following moderate fat meal				X																		
Plasma PK Sampling[5]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	<==========																					==========>
Con Med Review	<==========																					==========>
Furlough from Unit																					X	

HCV=Hepatitis C; BMI= Body mass index; ECG= Electrocardiogram; PK= Pharmacokinetic, SAD=single ascending dose

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. A single exam can be performed on D-2 or D-1.
2. A BMI does not need to be measured at the time of measurement.
3. Additional safety ECGs may be printed at the discretion of the PI if prolongation in QT interval is suspected. The frequency of ECGs will support an exploratory endpoint (should clinical development continue) to evaluate the exposure-response relationship between GSK3640254 and QTcF. Once human PK data (e.g. Cmax) are available, the number of ECG time points may be reduced in subsequent dosing groups. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order.
4. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
5. The number of PK sampling time points may be reduced in subsequent dosing groups once human PK data are available.

MAD Cohorts 3, 4, 5, 6 and the Expansion Cohort Screening

Procedure	Screening (up to 28 days before Day 1)
Outpatient Visit	X
Informed Consent	X
Inclusion/Exclusion Criteria and Demography	X
Medical/medication/ drug/alcohol history	X
Full Physical Exam[1]	X
CSSRS	X
Height, Weight, BMI	X
Vital signs	X
12 Lead ECG	X
Screening Holter	X
Drug/alcohol/cotinine screen	X
HbsAg, HCV, HIV tests	X
Hem/Chem/Urine tests	X
Pregnancy Test	X

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

MAD Cohorts 3, 4, 5, 6 and the Expansion Cohort On-Treatment

Procedure	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Follow-up (7-14 days post last dosing)
																0h	24h	48h	72h	96h	
Admission to Unit	X																				
Outpatient Visit																					X
Full Physical Exam[1]	X	X						X						X			X			X	X
CSSRS						X														X	
Weight, BMI[2]		X																			
Vital signs		X	X	X		X		X		X		X		X		X			X		X
12-lead safety ECGs	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X	X
Continuous ECG (full time matched baseline on Day-1)[3]		X	X	X												X	X				
Drug/alcohol/cotinine screen	X																				
Hem/Chem/Urine tests	X			X		X		X		X		X		X		X		X		X	X
Fasting Lipid test	X									X								X			X
Pregnancy Test	X																				X[4]
QD Dosing with GSK3640254 following moderate fat meal			X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Plasma PK Sampling[5]			X	X	X	X		X		X		X		X		X	X	X	X	X	
Plasma Metabolite Sampling[6]			X	X												X	X				

Procedure	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14 0h	Day 15 24h	Day 16 48h	Day 17 72h	Day 18 96h	Follow-up (7-14 days post last dosing)
Urine Metabolite Sampling[7]			X	X												X	X				
PGx Sampling (if participant consents)		X																			
Adverse Event Review	<==========																				==========>
Con Med Review	<==========																				==========>
Furlough from Unit																				X	

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. A single exam can be performed on D-2 or D-1.
2. A BMI does not need to be measured at the time of measurement.
3. ECG data extracted from the Continuous ECG will be assessed before PK sampling, prior to dosing and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4.5, 5, 5.5, 6, 8, 12 h, and 24 h post dose on Day 1 and Day 14 and on corresponding timepoints on Day -1. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order. The frequency of EKGs will support an exploratory endpoint to evaluate (should clinical development continue) the ER relationship between GSK3640254 and QTcF. Once human data (eg Cmax) is known, the number of EKG time points may be reduced.
4. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
5. Plasma PK samples for bioanalysis for GSK3640254 will be collected pre-dose according to the Time Window Allowances as indicated in the Study Reference Manual and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12 h on Day 1 and Day 14. On dosing days, plasma PK will be collected pre-dose. The number of PK sampling time points may be reduced in the initial MAD cohort as well as further in subsequent MAD dosing groups once human PK data are available in the SAD as well as in the initial MAD cohorts.
6. Plasma Metabolite samples for metabolite identification will be collected pre-dose according to the Time Window Allowances as indicated in the Study Reference Manual and at the same time points as for plasma PK samples on Day 1, Day 2 and Day 14, and Day 15. Plasma metabolite samples will not be collected in the expansion cohort.

7. Urine Metabolite Sampling for bioanalysis and metabolite identification will be collected pre-dose according to the Time Window Allowances as indicated in the Study Reference Manual and from time 0 up to 24 hours on Day 1 and Day 14. Urine samples will not be collected in the expansion cohort.

3. INTRODUCTION

3.1. Study Rationale

This is a double-blind (sponsor-unblinded), randomised, placebo-controlled, first-time-in-human (FTIH) study in a combined single- and multiple-dose protocol to investigate the safety, tolerability and PK of GSK3640254 in healthy participants. This study will enable further clinical development of GSK3640254, including a Phase IIA Proof of Concept (PoC) study in HIV-infected patients.

Infection with HIV-1 continues to be a serious health threat throughout the world, with more than one million infected individuals in the U.S. and more than 40 million worldwide. The now chronic exposure to combination anti-retroviral therapy (cART) has identified anti-retroviral (ARV)-associated long-term toxicities (e.g. central nervous system (CNS) or cardiovascular (CV)/metabolic effects, renal disease, etc.), creating a need to address and prevent these co-morbidities. Also, treatment failure remains a continuing concern in clinical care due to the presence and emergence of resistant strains and tolerability issues; in addition, the ageing HIV-1-infected population drives a need for drugs with fewer drug-drug interactions. In this environment, medicines with novel mechanisms of action (MoA) that can be used as part of the preferred cART regimen have an important role to play. However, to be successful, a new ARV agent must be safe, effective, provide a relatively high barrier to resistance, have low toxicity, have minimal drug-drug interactions, and preferably be a relatively low-dose once-a-day drug that can be combined with other agents as part of a fixed-dose regimen. GSK3640254, an HIV-1 maturation inhibitor, has the potential to meet such valued features for a new ARV medicine.

3.2. Background

The inhibition of maturation and release of human immunodeficiency virus-1 (HIV-1) is a novel target for drug development, distinct from viral protease, reverse transcriptase or integrase. There are no MIs approved for the treatment of HIV infection. GSK3640254 is a MI that displays *in vitro* evidence of low nanomolar potency against multiple HIV-1 Gag polymorphisms and a broad spectrum covering multiple HIV-1 subtypes, supporting compound development.

GSK3640254 is a next-generation HIV MI which is improved over existing/prior developmental MIs in the following ways: (1) it exhibits significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that GSK3640254 exhibits a higher barrier to emergence of resistant viruses (except for A364V); (3) GSK3640254 has improved potency *in vitro* toward all HIV-1 subtypes; and (4) it has a projected lower once-daily (QD) human dose (see dose rationale). Summaries of the pre-clinical studies are included in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number 2016N294821_00].

3.2.1. Background Key Safety and PK data with a Prior Maturation Inhibitor (GSK3532795)

Bristol-Myers Squibb (BMS), and later VH, developed a HIV-1 MI (GSK3532795), which was studied through Phase 2b studies in both treatment-naïve (AI468038) and experienced (AI468048) HIV-1 infected adults. In study AI468038, a greater number of participants who received GSK3532795 experienced gastrointestinal (GI) intolerability (specifically G1-2 diarrhoea and abdominal pain). A detailed examination of all GI adverse events (AEs) (regardless of Grade/Relationship) revealed a relationship with dose [GlaxoSmithKline Document Number 2016N302783_00]. Ultimately, the rate of GI intolerability in the GSK3532795 dose groups in the Phase 2b study AI468038, helped lead to VH's decision to end all trials and not progress to Phase 3 studies.

GI AEs were also previously observed in healthy participants in Phase 1 studies with varying doses, durations, and formulations of GSK3532795. First, in AI468049, the rates of GI AEs ranged from 33-67% across cohorts (single oral doses of GSK3532795 60 mg – 180 mg with food). Second, in AI468063, 65% of participants receiving GSK3532795 180 mg QD with food developed diarrhea. Finally, in AI468052, 29% of participants who received GSK3532795 180 mg QD with food developed GI AEs. In all three studies, the most common GI AEs were abdominal pain and diarrhoea.

Aside from mild-moderate GI intolerability, two serious adverse events (SAEs) occurred in phase I study AI468044: one healthy participant had acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The two participants received GSK3532795 240 mg twice daily (BID) and 240 mg QD for 3 days with food, respectively. These events were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric AEs in studies with GSK3532795 were headache, dizziness and sleep abnormalities (e.g. insomnia, abnormal dreams).

The PK of GSK3532795 has been characterized in healthy participants at single doses from 10 mg to 180 mg and at multiple doses ranging from 10 mg to 240 mg, as well as at doses ranging from 5 mg to 180 mg in HIV-1-infected participants. These doses were administered as various formulations (spray-dried dispersion suspension, micronized and non-micronized crystalline tablets and suspensions), as single and/or multiple doses, with and without food. Under fasted conditions, exposures to GSK3532795 increased in a less-than-dose-proportional manner with significant overlap in exposures at doses ≥80 mg, likely due to the limited solubility of GSK3532795. The effect of food was minimal at lower doses (≤40 mg); however, following a single oral dose of 180 mg GSK3532795 with food, exposures increased approximately 2-fold relative to fasted conditions. Assessment of data across multiple clinical trials suggested that administration of GSK3532795 with food resulted in dose-proportional increases in exposure up to doses of 240 mg and that food was necessary to achieve target efficacious concentrations of GSK3532795.

3.2.2. Preliminary Safety and PK data in Current Study (SAD doses 1 - 700 mg and MAD doses 50 – 200 mg daily)

Overall, there have been no major clinical safety/tolerability findings in the SAD (single doses up to 700 mg) or MAD (14 days of dosing up to 200 mg) through May 7, 2018. There have been 20 subjects treated in the blinded SAD and 33 subjects treated in the blinded MAD. Preliminary ongoing data review show no deaths or SAEs. There have been 4 individual AEs leading to discontinuation from the trial:

- Blinded SAD 10 mg arm: Depression (Grade 2, not related).
- Blinded SAD 10 mg arm: Viral Infection (Grade 1, not related) lasting two days
- Blinded SAD 100 mg arm: Viral Infection (Grade 1, not related) lasting seven days
- Blinded MAD 200 mg arm: Rash Maculopapular (Grade 1, related). This rash occurred 8 days after receiving study medication and lasted for 6 days. There were no laboratory abnormalities. A Dermatology Consultant concluded this was a drug rash and the subject later received fexofenadine 180 mg once daily with a topical steroid cream.

There have been 10 individual AEs related to study medication (9 Grade 1; One Grade 2):

- Blinded SAD 10 mg arm: Dizziness
- Blinded SAD 30 mg arm: Diarrhea and Abdominal Pain
- Blinded SAD 700 mg arm: Diarrhea
- Blinded MAD 50 mg arm: Headache (the only G2 related AE), Fatigue, and Transaminases Elevated. The subject with elevated transaminases had peak ALT of 83 IU/L on Day 16 after study medication. The remaining LFTs were normal throughout. An Ultrasound showed a subcapsular area of heterogenous echogenicity within segment 7, measuring approximately 35 x 23 x 36 mm. A follow up MRI was normal.
- Blinded MAD 200 mg arm: Lethargy, Nausea, and Rash Maculopapular.

Preliminary review of blinded safety data (see Table 1) for the SAD 1 - 700 mg doses show 17 subjects experienced 60 individual AEs (58 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System (16 individual AEs) and Gastrointestinal Disorders (11 individual AEs). The most frequent AEs have been Headache (10 individual AEs), Diarrhea and Contact Dermatitis (5 individual AEs each), and Dizziness (4 individual AEs). There were four Psychiatric individual AEs (three of which have occurred at 1 and 3 mg single blinded arms): Depression, Insomnia, and Nightmare (two individual AEs). There were no Cardiac AEs. There has been no dose/AE relationship.

Preliminary review of blinded safety data (see Table 2) for the MAD 50 – 200 mg (Daily for Fourteen Days) show 23 subjects experienced 79 individual AEs (77 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System (25 AEs) and Gastrointestinal Disorders (12 individual AEs). The most frequent AEs have been

Headache (11 individual AEs), Dizziness (6 individual AEs), and Fatigue (5 individual AEs). There has been no clinically relevant GI or neurologic AE/dose relationship. One subject in the blinded 200 mg arm accounted for 13 individual AEs (5 of which were in the Neurologic SOC). There were three Psychiatric individual AEs: Agitation, Abnormal Dreams, and Nightmare. There was one Cardiac AE (palpitations in the 200 mg blinded dose).

There were no clinically significant abnormal fluctuations or trends in vital signs in the SAD or MAD. There were no abnormal clinically significant arrhythmias or QTcF prolongations observed for any subject in the SAD or MAD. There were no laboratory abnormality trends across doses that were clinically significant or associated with any symptoms.

Table 1 Summary Table (all AEs) in blinded SAD 1 - 700 mg doses

		AEs by Blinded SAD Cohort/Period							
SOC	**PT**	**1 mg**	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**200 mg**	**400 mg**	**700 mg**
Nervous System Disorders	Dizziness	1	1	1					1
	Headache	1		1	2	2	2	2	
	Parasthesia			1					
	Migraine			1					
Gastrointestinal Disorders	Vomitting					2			
	Feces Soft	1							
	Diarrhea			1	1	2			1
	Abdominal Pain				1				
	Feces Discolored					1			
	Feces Pale							1	
Infections and Infestations	Nasopharyngitis			1		1		1	
	Oral Herpes				1				
	Viral Infection			1		1			
	Upper Respiratory Tract Infection						1		
Respiratory, Thoracic, and Mediastinal Disorders	Nasal Obstruction			2					1
	Cough			1		1			
	Oropharyngeal Pain							1	
	Hemoptysis							1	
Skin and Subcutaneous Disorders	Contact Dermatitis	1	1	1			1	1	

		AEs by Blinded SAD Cohort/Period							
SOC	**PT**	**1 mg**	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**200 mg**	**400 mg**	**700 mg**
Psychiatric Disorders	Depression	1							
	Insomnia	1							
	Nightmare		1						1
Injury, Poisoning, and Procedural Complications	Face Injury	1							
	Skin Abrasion						1		
	Contusion			1					
	Limb Injury	1							
General Disorders and Administration Site Conditions	Catheter site pain			1					
	Vessel Puncture Site Bruise		1						
	Chest Pain	1							
Investigations	Transaminases Increased						1		1
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal Pain				1				
Total AEs by Blinded SAD Cohort/Period		9	4	13	6	10	6	7	5

Table 2 Summary Table (all AEs) in blinded MAD 50 – 200 mg doses

		AEs by Blinded MAD Cohort/Period		
SOC	**PT**	**50 mg**	**100 mg**	**200 mg**
Nervous System Disorders	Dizziness	1	2	3
	Headache	4	2	5
	Somnolence	1		
	Disturbance in Attention			2
	Lethargy			2
	Dizziness Postural			1
	Hypoaesthesia			1
	Dysgeusia			1
Gastrointestinal Disorders	Lip Dry	1		
	Mouth Ulceration	1		

		AEs by Blinded MAD Cohort/Period		
SOC	**PT**	**50 mg**	**100 mg**	**200 mg**
	Aphthous Ulcer	1		
	Abdominal Pain	1		1
	Abdominal Distention		1	1
	Glossodynia			1
	Constipation			2
	Nausea			1
	Gastroesophageal Reflux Disease			1
General Disorders and Administration Site Conditions	Catheter site pain			1
	Vessel Puncture Site Bruise		1	1
	Fatigue	2	2	1
	Feeling Cold	1		
	Catheter site Bruise			1
Skin and Subcutaneous Disorders	Contact Dermatitis	1		2
	Blister		1	
	Dry Skin		1	
	Rash			1
	Rash Maculopapular			1
	Pruitis			1
Musculoskeletal and Connective Tissue Disorders	Back pain	1	1	2
	Musculoskeletal Stiffness	1		
	Muscle Twitching		1	
Injury, Poisoning, and Procedural Complications	Laceration			1
	Contusion	1	1	2
Infections and Infestations	Hordeolum		1	
	Abscess		1	
	Oral Herpes			1
Psychiatric Disorders	Agitation		1	
	Abnormal Dreams			1
	Nightmare		1	

		AEs by Blinded MAD Cohort/Period		
SOC	**PT**	**50 mg**	**100 mg**	**200 mg**
Ear and Labyrinth Disorders	Ear Discomfort			1
	Excessive Cerumen Production			1
Renal and Urinary Disorders	Pollakiuria			1
	Dysuria			1
Respiratory, Thoracic, and Mediastinal Disorders	Epistaxis	1		
Investigations	Transaminases Increased	1		
Cardiac Disorders	Palpitations			1
Total AEs by Blinded MAD Cohort/Period		19	17	43

Preliminary PK parameters for GSK3640254 following single dose administration from 1 to 700 mg are summarized in Table 3. GSK3640254 is slowly absorbed with maximum concentration observed on average 3-4 hours after dosing and slowly eliminated with an average half-life of 24 hours. Cmax and AUC increased in a close to dose proportional manner from 1 to 400 mg with a plateauing in exposure at the 700 mg dose. The maximum observed mean Cmax for the single dose administration (Table 3) is 1881 ng/mL at the dose of 400 mg. The maximum observed mean AUC(0-inf) for the single dose administration (Table 3) is 43116 ng.hr/mL at the dose of 400 mg. The mean exposure observed at 700 mg is slightly lower than that at 400 mg single administration and thus we anticipate similar exposures with doses greater than 700 mg.

Table 3 Summary of Preliminary PK Parameters Following Single Doses of GSK3640254 in study 207187

	Dose							
	1 mg	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**200 mg**	**400 mg**	**700 mg**
PK Parameter	**Geometric Mean (CV%) [N]***							
Cmax	4.9 (16) [6]	13.8 (31) [6]	47 (30) [6]	129.8 (21) [6]	372.1 (72) [6]	578.9 (27) [6]	1881 (50) [6]	1760.8 (44) [6]
Tmax	3.5 (2.5-6) [6]	4.5 (2-5) [6]	3.5 (2.5-5) [6]	4 (2.5-5) [6]	3.8 (2-5) [6]	3 (2-4) [6]	3.3 (2-6) [6]	3.3 (2-4.5) [6]
T1/2(z)	NC	22 (14) [6]	25.8 (17) [6]	23.3 (16) [6]	23.9 (14) [6]	23.2 (17) [6]	23.3 (16) [6]	22.2 (28) [6]
AUC	NC	340 (29) [6]	1229.3 (19) [6]	3008 (26) [6]	8566.4 (67) [6]	14978 (41) [6]	43115.7 (52) [6]	39972.5 (50) [6]
* Tmax has been reported as Median (Min - Max)								
AUC represents AUC(0-inf); NC: Not Computed								
Units: Cmax in ng/mL, AUC in ng.h/mL, t1/2 and tmax in hours								

Preliminary PK parameters on Day 1 and Day 14 for GSK3640254 following repeat dose administration of 50, 100 and 200 mg for 14 days are summarized in Table 4. The exposures on Day 14 are on average 2-3 folds higher than that on Day 1. Cmax and AUC on Day 14 tended to increase in a close to dose proportional manner from 50 to 200 mg. The maximum observed mean Cmax for the repeat dose administration is 1528 ng/mL at the dose of 200 mg on Day 14. The maximum observed mean AUC(0-24) for the repeat dose administration is 23046 ng.hr/mL at the dose of 200 mg on Day 14.

The anticipated mean Cmax at a proposed dose of 320 mg based on the observed exposures (Table 4) using a dose proportionality model is predicted to be 1030 ng/mL on Day 1 and 2475 ng/mL for Day 14. The anticipated mean AUC(0-24) on Day 14 at a proposed dose of 320 mg based on observed exposures (Table 4) using a dose proportionality model is predicted to be 37942 ng.hr/mL. The probability of any subject exceeding the PK stopping criteria for MAD study with the dose of 320 mg repeat dosing, which is AUC(0-24) of 61100 ng.hr/mL based on LOAEL exposure in rat at 30 mg/kg, is 42% based on data collected through 9th May. The probability of any subject exceeding the PK stopping criteria for SAD study with the dose of 320 mg repeat dosing, which is a Cmax of 7960 ng/mL based on minimal QT effects observed in one dog, is 0.7% based on data collected through 9th May.

Table 4 Summary of Preliminary PK Parameters Following Repeat Dose administration of GSK3640254 in study 207187

	Day 1			Day 14		
	Dose			Dose		
	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
PK Parameter	**Geometric Mean (CV%) [N]***					
AUC (0-24)	2867.4 (30) [6]	6826.2 (23) [6]	8947.1 (49) [NP]	6285.6 (34) [6]	17537.5 (14) [6]	23046.2 (36) [NP]
Cmax	214.5 (24) [6]	535.6 (23) [6]	689.2 (40) [NP]	413.5 (32) [6]	1182 (10) [6]	1528.4 (30) [NP]
T1/2(z)	NC	NC	NC	24.5 (8) [6]	28.6 (19) [6]	21.9 (12) [NP]
Tmax	3.8 (3-5) [6]	4.3 (2-5) [6]	4 (1.5-5.5) [NP]	3.8 (2.5-5) [6]	4 (1.5-4.5) [6]	3.5 (2-5) [NP]
* Tmax has been reported as Median (Min - Max)						
Units: Cmax in ng/mL, AUC in ng.h/mL and Tmax in hours						
NP: Not Printed as the expansion cohort is still running. This includes 6 active subjects from Cohort 5 and the subjects from expansion cohort 7 studied thruMay 9th, 2018.						
NC: Not Computed						

3.3. Benefit/Risk Assessment

Based upon pre-clinical studies, the major risks are GI intolerability (e.g. abdominal pain and diarrhoea), prolongation of QTc, and neuropsychiatric safety. Reproduction of preclinical GI toxicity findings (e.g. single-cell parietal cell necrosis) would be unlikely during the limited dosing of GSK3640254 in this study. As noted in Section 3.3.1, one pre-clinical study did show one dog with an increased QTc interval when given a single dose of GSK3640254. Finally, the protocol will exclude potential participants from either SAD or MAD with any pre-existing psychiatric condition or positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS. The CSSRS assessment will also be administered by a clinician (or qualified designee) during the on-treatment portion of the MAD only.

Thus, to ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, and neuropsychiatric safety), this clinical trial will include healthy adults who will receive frequent clinical, ECG, and laboratory evaluations in-house during their participation in the trial.

The clinical data gathered through May 7, 2018 is summarized in Section 3.2.2 Overall, there have been no major clinical safety/tolerability findings in the SAD (single doses up to 700 mg) or MAD (14 days of dosing up to 200 mg). The proposed amendment seeks to evaluate a higher dose (320 mg Daily) in the MAD. The probability of the AUC(tau) exceeding the established PK stopping criteria is 42%. Subjects recruited for the 320 mg QD dose in Cohort 6 will have the same inclusion/exclusion criteria, have the same study

and subject stopping criteria, and undergo the same safety evaluation. Based upon the preliminary safety and PK data gathered to date (see Section 3.2.2) subjects will be adequately monitored.

ViiV Healthcare has assessed this study for any risks that may be posed to participants taking part. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMEA) guidance on strategies to identify and mitigate risks for FTIH clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/XX).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3640254 may be found in the CIB [GlaxoSmithKline Document Number 2016N294821_00].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Pre-clinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with cDNA from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in QT interval (up to 20 ms) occurred primarily in one dog given 17 mg/kg. Later, there were no GSK3640254-related effects on ECG parameters in dogs given up to 25 mg/kg/day for 4 weeks.	Protocol exclusion criteria based on screening Holter and ECG parameters and cardiac medical history. Participants in the SAD/MAD will have a 24 hour holter monitor during the screening period and continuous ECGs during treatment; they will also have frequent clinical and VS evaluations (see SoA table).
Gastrointestinal intolerability and toxicity	Clinical signs indicative of gastrointestinal intolerability (sporadic vomiting and abnormal faeces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. These findings were reversible. Finally, GI intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing.	Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms Participants in the SAD and MAD will undergo intensive physical exam and laboratory testing. In addition, participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs. Finally, a general GI toxicity evaluation and monitoring plan will be available to guide the PI should GI AEs emerge (See Section 9.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Neurologic/psychiatric safety	Two psychiatric SAEs in previous MI GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) at supratherapeutic doses were seen in healthy subjects in TQT study. From a Neurologic and Psychiatric AE summary and PK/PD analysis for GSK3532795 across all studies mild G1 headache and G1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and P2b studies). No exposure-response relationship seen for select neurologic and psychiatric AEs (based on TQT and P2b studies) CNS penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low brain distribution/penetration	Protocol exclusion criterion based on any pre-existing psychiatric condition (including assessment using the CSSRS) for participants in both the SAD and MAD. Participants in the SAD and MAD will undergo intensive physical exam and laboratory testing. In addition, participants will undergo continuous evaluation for adverse events during their participation in the trial; there are clinical stopping criteria based upon incidence and intensity of treatment-emergent AEs. Subjects will be housed throughout the MAD 14day component to ensure rapid diagnosis and management of any potential event. Finally, participants in the MAD only will have assessment via a clinician (or qualified designee) administered CSSRS during the on-treatment portion of the study. In the event of a positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

3.3.2. Benefit Assessment

This is a study in healthy participants; no medical benefit will be derived by volunteers' participation.

3.3.3. Overall Benefit:Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the preliminary clinical data gathered through May 7, 2018 and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable.

3.3.4. Acute Monitoring in FTIH Studies

Consistent with GSK/VH Guidance and CHMP guidelines for early phase studies, the study will be conducted in an accredited Phase 1 Clinical Research Unit with previous experience with first-time-in-human trials and immediate access to hospital facilities for the treatment of medical emergencies.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of GSK3640254 following single and repeated daily administration	• GSK3640254 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
Secondary	
• To describe the PK of GSK3640254 following single and repeated daily administration	• GSK3640254 PK parameters: Part 1 (single dose): AUC(0-24), AUC(0-tlast), AUC(0-inf), Cmax, C24, tmax, tlag, t1/2, Clast, tlast, CL/F. Part 2 (Repeated QD doses for 14 days): Day 1: AUC(0-24), Cmax, C24, tmax, tlag Day 14: AUC(0-τ), Cmax, Cτ, tmax, t1/2, and CL/F
• To examine dose proportionality following single and repeated doses of GSK3640254	• GSK3640254 Single dose: AUC (0-inf), Cmax. Repeat dose AUC(0-τ), Cmax, Cτ
• To assess accumulation of GSK3640254	• Accumulation ratios: R AUC(0-τ), R (Cmax), R (Cτ)
• To assess time to steady-state of GSK3640254	• Pre-dose concentrations on Day 2-14 (Part 2)
Exploratory	
• To assess the exposure response relationship between GSK3640254 and safety parameter, including QTcF following single and repeated administration	• Change-from-baseline QTcF (ΔQTcF)
• To investigate the biotransformation of GSK3640254 in plasma and urine	• Provide samples of plasma and urine for the identification of any compound-derived metabolite(s)
• As available, to assess the impact of food on the PK of GSK3640254	• GSK3640254 single dose Cmax, AUC(0-inf), and C24

AUC(0-24) = Area under the plasma concentration time curve from zero to 24; AUC(0-inf) = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; Cmax= Maximum observed concentration; tmax= Time of occurrence of Cmax; t1/2= Apparent terminal phase half-life; CL/F= Apparent oral clearance

Note: The exploratory endpoints may be analyzed once GSK3640254 clinical development continues.

5. STUDY DESIGN

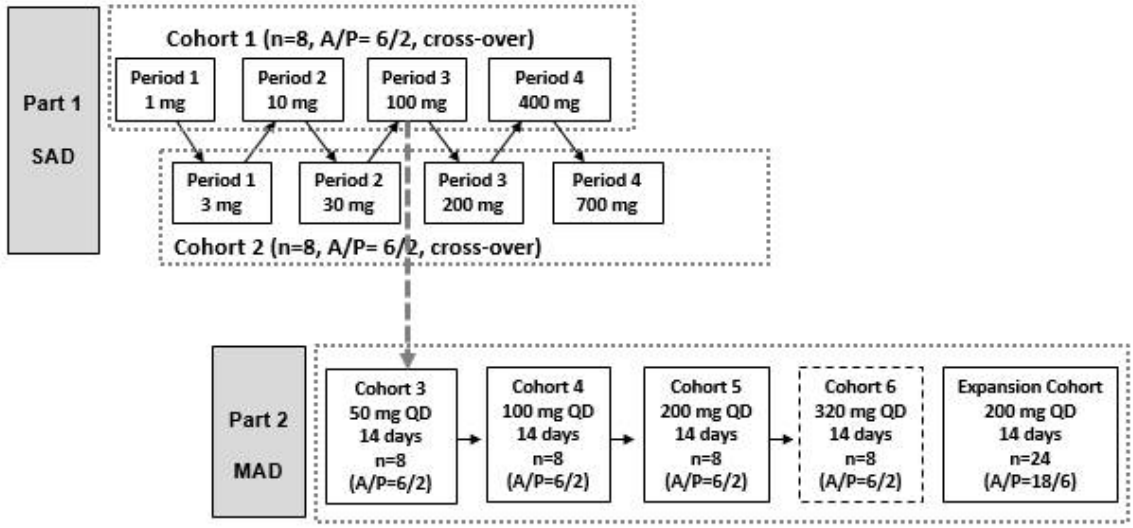
5.1. Overall Design

This study is a Phase 1, double-blind (sponsor-unblinded), randomized, placebo-controlled, single- and repeat-dose escalation study to investigate the safety, tolerability, and PK of GSK3640254 in healthy participants. Approximately 72 healthy participants will be randomized in one of two parts: Part 1 (SAD) and Part 2 (MAD). The total number of cohorts in the SAD will be two; the total number of cohorts in the MAD will be five. The entire trial will be conducted in an inpatient clinical trial unit.

A summary of the overall study design, including proposed doses, sample size, and order, is presented in Figure 2; **SoA** tables are included in Section 2.

As described in detail below, the proposed dosing schedule is designed to investigate single doses of GSK3640254 initially in Part 1 and then, at a suitable cross-over point, begin repeated once-daily dosing of GSK3640254 in Part 2. All doses will be administered immediately following a moderate fat meal (approximately 600 calories with approximately 30% of calories from fat), unless otherwise indicated.

Figure 2 Phase 1 Study in Healthy Participants using planned doses of GSK3640254



Note: A=active, P=placebo. The doses shown here were/are being completed. Amendment 04 proposes to evaluate a 320 mg Daily dose in MAD Cohort 6.

Study Design Details Part 1 (SAD):

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts of eight healthy participants each. Each of these two cohorts will contain up to four escalating doses of GSK3640254. The interlocking design as shown in Figure 2 and the randomization sequence in Table 5 will allow the 8 participants in each Cohort

to potentially receive one of the two lowest and one of the two highest doses of GSK3640254. In each escalating period and Cohort, 6 participants will be randomized to GSK3640254 and 2 participants will be randomized to placebo. Details of the starting dose and dose escalation can be found in Section 5.5.3.

Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses (Table 5). Two participants in either Cohort will be assigned to one of the four treatment sequences, and each participant will receive placebo once.

Table 5 Description of treatment sequences in Cohort 1 and Cohort 2

Cohort 1	Period 1	Period 2	Period 3	Period 4
Sequence 1	Placebo	Dose 3	Dose 5	Dose 7
Sequence 2	Dose 1	Placebo	Dose 5	Dose 7
Sequence 3	Dose 1	Dose 3	Placebo	Dose 7
Sequence 4	Dose 1	Dose 3	Dose 5	Placebo

Cohort 2	Period 1	Period 2	Period 3	Period 4
Sequence 1	Placebo	Dose 4	Dose 6	Dose 8
Sequence 2	Dose 2	Placebo	Dose 6	Dose 8
Sequence 3	Dose 2	Dose 4	Placebo	Dose 8
Sequence 4	Dose 2	Dose 4	Dose 6	Placebo

Part 1 SAD: Sentinel Dosing

To conservatively assess safety, at the start of each dose period of the SAD, 2 out of the 8 participants will serve as sentinel participants with one receiving GSK3640254 and the other receiving placebo. These sentinel participants will be followed clinically for 24 hours after dose administration to monitor for emergence of adverse events. If there are no safety concerns, in the judgment of the PI, on review of the 24-hour safety data (e.g. vital signs, ECGs, and adverse events) for the sentinel participants, the remaining 6 participants will subsequently be administered either GSK3640254 or PBO according to randomization schedules.

Part 1 SAD: Dose Escalation

Dose escalation in Part 1 will be determined by the VH/GSK study team and the PI 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 as well as the SAD PK stopping criteria (see 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):

Part 2 consists of four ascending repeat-dose cohorts (Cohorts 3 to 6), each with 8 participants (active/PBO=6/2) who will receive a once-daily dose of GSK3640254 or PBO for 14 days. Details of the starting dose and dose escalations in Part 2 (MAD) are provided in Section 5.5.4.

The earliest point at which Part 2 (MAD) of the study will be initiated is 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 GSK3640254, noted as X, is anticipated to be that which is predicted to provide a steady state Ctrough $\geq$ 0.11 μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1 (see Section 5.5.2 for further details). The initial dose in the MAD (Cohort 3) will be approximately half the anticipated minimally effective dose or 0.5X. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1). However, as a plateau in exposure has been seen in the SAD between 400 mg and 700 mg, the highest dose in the MAD may be evaluating steady-state Cmax concentrations that are up to 50% greater than previously observed in the SAD while not exceeding AUC already explored in the SAD. The 320 mg QD dose Cmax on Day 14 will not exceed the SAD PK stopping criteria (see Section 8).

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 four participants in current cohort receiving active drug will be required for dose escalation.

Part 2 also includes an Expansion Cohort which was conducted at the conclusion of Cohort 5. VH's prior and structurally similar MI (GSK3532795) ceased development in Phase 2b (due in part to a higher proportion of participants experiencing GI intolerability). GSK3532795, studied in Phase 1 studies of normal healthy volunteers showed diarrhoea of up to 65%. The Expansion Cohort will evaluate the rate of GI intolerability in 24 participants (active/PBO =18/6). The dose studied (200 mg) was previously studied doses in the MAD and did not meet safety or PK stopping criteria. While no formal statistical testing will be performed, a summary of GI AEs will be provided from: 1) 24 participants receiving one of the GSK3640254 doses studied

previously and 2) 14 participants receiving placebo across the entire MAD. These numbers of participants should provide sufficient clinical inference and better estimation of GI AEs frequency at a given dose (which can be used to inform subsequent dose selection/therapeutic index for HIV-1 infected participants).

Participants in both Part 1 and Part 2 will have a screening visit within 30 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 12 weeks.

5.2. Number of Participants

A total of approximately 72 healthy participants will be randomized in the trial: SAD (n~16) and MAD (n ~56).

If participants prematurely discontinue the study in the SAD, they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment sequence where the prior participant prematurely discontinued. Previously administered doses will not be repeated by replacement subjects if dose escalation criteria are met.

If participants prematurely discontinue the study in the MAD, they may be replaced at the discretion of the Sponsor in consultation with the investigator. The replacement participants will be assigned to the same treatment in the same Cohort where the prior participant prematurely discontinued.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

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

5.4. Scientific Rationale for Study Design

This study is a first time in human (FTIH) study that will assess the safety, tolerability, and PK of GSK3640254, an HIV-1 MI. The data gathered will inform subsequent clinical trials for GSK3640254, including a Phase 2a POC study in HIV-1-infected participants.

All doses of GSK3640254 in this study will be administered in the fed state, with dosing occurring within 5 minutes of completing a moderate fat meal, unless noted otherwise. Data with a previous MI, GSK3532795, demonstrated that food was necessary to achieve dose proportional PK and target efficacious concentrations (see Section 3.2.1). Given the structural similarities, including solubility limitations, between GSK3532795 and GSK3640254, administration of GSK3640254 with food in this study is expected to enhance both bioavailability and the likelihood for linear PK, allowing for a rigorous assessment of safety and tolerability across a larger exposure range than would be allowed in the fasted state. Finally, VH intends to administer GSK3640254 in the fed

state in a future Phase 2a POC study in HIV-infected participants; the current study will assess the safety, tolerability, and PK of GSK3640254 under the same conditions in healthy participants prior to dosing in HIV-infected participants. The impact of food on exposures to GSK3640254 will be assessed in a future Phase 1 study in healthy participants during clinical development.

In Part 2 of the study (MAD), doses potentially up to 4 times the minimally anticipated effective dose (~ 80 mg QD) are planned to be evaluated. In future studies in HIV-1-infected participants, these doses/exposures may be evaluated to understand the relationship between GSK3640254 exposures and efficacy, duration of response, and resistance development (see Section 5.5.2). Furthermore, assessment of this dose/exposure range (anticipated to be the therapeutic exposure range in the target population) in healthy participants will inform safety and tolerability prior to exposing a more vulnerable HIV-1-infected population to GSK3640254 and will inform risk mitigation strategies for potential drug interactions.

This dose/exposure range in healthy participants is clinically reasonable based upon the preclinical profile of GSK3640254, the clinical profile of a prior MI (GSK3532795), and the planned inpatient evaluation for treatment emergent risks: including QT prolongation, GI intolerability/toxicity, and neuropsychiatric safety – which will frequently be monitored in this limited dosing duration setting.

5.5. Dose Justification

5.5.1. Predicted Human Pharmacokinetics

The pharmacokinetic profile for GSK3640254 in humans was predicted using allometric scaling across all species (mouse, rat, dog, and monkey), and was combined with Css-MRT modeling to obtain the predicted human PK profile. Using this method, the IV plasma clearance in humans for GSK3640254 was projected to be low (0.47 mL/min/kg). The intravenous volume of distribution was assumed to be the same as in dogs or close to total body water (0.5 L/kg). The elimination half-life was anticipated to be around 15 hours, leading to a small anticipated accumulation with once daily dosing of ~50%. The mean oral bioavailability in animals was 58% and assumed for exposure projections in humans.

The emerging PK data are presented in Section 3.2.2.

5.5.2. Predicted Human Effective Dose

Steady-state trough concentrations are typically the PK parameter of interest for efficacy for other antiretroviral classes such as protease inhibitors and integrase inhibitors. The minimum target steady state trough level for GSK3640254 was established using a value of 3 times the protein binding-adjusted EC_{90} (3xPBA-EC_{90}) for one of the least sensitive variants, a triple-mutant polymorph (R361K/V362I/L363M), from a library of 36 gag/pr genotyped viruses. This virus exhibited EC50, EC90 and 3x PBA EC90 values of 3, 7 and 150 nM (0.11 µg/mL), respectively. This 3xPBA-EC_{90} represents the anticipated minimal effective trough concentration of GSK3640254.

The potential minimally effective dose for GSK3640254 was initially estimated using the predicted human PK profile, assuming similar between-participant PK variability to that observed with GSK3532795 (Population PK model based on data from Phase 2b study AI468038, Metrum Research Group, 2016), to ensure that 95% of participants have steady state trough concentrations that exceed the target concentration of 0.11 µg/mL following once daily dosing of GSK3640254. This led to the prediction of a likely minimally effective once daily dose of approximately 40 mg, assuming 58% bioavailability. Following single administration of 1, 3 and 10 mg of GSK3640254 in this study, a pharmacokinetic model was fit through the concentration-time data and these population PK parameters were used along with the previously assumed PK variabilities. The updated minimally effective once daily dose was approximately 70 mg. At this dose, the mean repeat-dose Cmax is predicted to be approximately 0.544 µg/mL, mean trough concentration is predicted to be approximately 0.238 µg/mL and mean AUC is predicted to be approximately 8.91 µg.h/mL (Table 8). The anticipated steady-state mean AUC is 2.52-fold lower than the NOAEL in the rat, 6.86-fold lower than the LOAEL in the rat, and 8.23-fold lower than the LOAEL in the dog. The population PK model was further updated with all the concentration-time data available up to 9 May 2018 (excluding the 700 mg SAD dose) and the population PK parameters including the between subject variabilities were used to provide the updated minimally effective once daily dose of approximately 80 mg.

The relationship between GSK3640254 exposure and efficacy, duration of antiviral response, and development of on-treatment resistance will be evaluated in future studies in HIV-1-infected participants where assessment of a range of exposures will be important to inform the therapeutic dose range of GSK3640254. One exposure parameter of interest is inhibitory quotient (IQ), where IQ = Ctrough/PBA-EC_{90}. The IQs of other antiretrovirals at approved doses are approximately 19, 27, and 36 for dolutegravir 50 mg once daily, atazanavir 300 mg once daily with ritonavir, and lopinavir 400 mg twice daily with ritonavir, respectively [Van Lunzen, 2012 and Zhu, 2012]. For GSK3640254, the minimally effective dose provides a trough concentration of 0.11 ug/mL at steady state in 95% of the participants and represents a geometric mean IQ of 7.92. To facilitate assessment of a range of GSK3640254 IQs in future studies in the target population, doses up to 4 times those of the minimally effective dose are planned for assessment in Part 2 (MAD) in healthy participants. These doses will be administered in accordance with PK and safety stopping criteria (see Section 8.1.3). Projected exposures at the highest anticipated once daily dose in the MAD include a mean repeat-dose Ctrough of 1.02 ug/mL and an IQ of 27.8.

5.5.3. Part 1 (SAD) Starting Dose and Dose Escalation

The starting oral dose of GSK3640254 in the SAD will be 1 mg. Assuming a 10-fold safety factor and a body weight of 60 kg, this starting dose is lower than that calculated based on the NOAEL in rat of 10 mg/kg (maximum recommended starting dose (MRSD) = 9.6 mg) and the lowest observed adverse effect level (LOAEL) in dog of 1 mg/kg (MRSD = 3.24 mg), in the absence of a no observed adverse effect level (NOAEL) in dog [Guidance for Industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. FDA/CDER, July 2005]. Although a NOAEL was not established in the 4-week dog study due to the presence of gastric toxicity at all

doses, the gastric findings at 1 mg/kg/day (LOAEL) were minimal in severity, reversible, and observed in only one dog.

Based on the predicted human PK, a 1 mg dose would provide a mean AUC(0-inf) of 0.343 μg.h/mL and a mean Cmax of 0.0197 μg/mL. This predicted AUC(0-inf) is 65-fold lower than that observed in the rat at the NOAEL, 178-fold lower than that observed in the rat at the LOAEL, and 214-fold lower than that observed in the dog LOAEL.

Dose escalations in Part 1 (SAD) will be governed in real-time by safety and PK stopping criteria (see Section 8.1.3 and Section 8.1.4). A dose will not be assessed in the MAD until the anticipated steady-state exposures (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met PK or safety stopping criteria in the SAD portion of the study (Part 1). The maximum dose in the MAD is planned to be approximately 4X, where X is the minimally efficacious dose given once daily (see Section 5.5.2). To account for anticipated accumulation of 115% upon repeat dosing, the highest dose in the SAD will be approximately 9X. This will allow single dose evaluation of the highest anticipated steady-state exposures before once daily administration of the highest MAD dose. Based on the assumptions described above, the anticipated maximum dose in Part 1 is a single dose of up to 700 mg. The predicted mean single dose Cmax of 700 mg is 2.74 μg/mL. Given different assumptions of with-in and between participant Cmax variability, the probabilities of any participant Cmax being above 7.96 μg/mL, the SAD PK Stopping Criterion (Section 8.1.3), are illustrated in 6. All doses in the SAD are governed by safety and PK stopping criteria. A dose which has met formal clinical, QT, or PK stopping criteria will not be repeated in the SAD (or MAD).

Table 6 Probability of any SAD participant (Cmax >7.96 µg/mL) for potential doses

Cmax Variability		Potential GSK3640254 SAD Doses				
%CVw[1]	%CVb[1]	30mg	100mg	200mg	400mg	700mg
7.5	15	0	0	0	0	0
15	15	0	0	0	0	0.001
12.5	25	0	0	0	0	0.005
25	25	0	0	0	0	0.038
17.5	35	0	0	0	0.001	0.071
35	35	0	0	0	0.01	0.191
25	50	0	0	0	0.024	0.261
50	50	0	0	0.007	0.094	0.445

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

5.5.4. Part 2 (MAD) Starting Dose and Dose Escalation

The initial dose in the MAD (Cohort 3) will be approximately half the likely minimally effective dose, re-estimated based on the clinical PK data collected in the early doses of Part 1. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts, and will be governed by both safety and MAD PK stopping criteria (see Section 8.1.3 and Section 8.1.4). Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any participant AUCtau in the MAD above 61.1 µg.hr/mL, the MAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table 7.

Table 7 Probability of any MAD participant (AUCtau > 61.1 µg.h/mL) for potential QD doses

AUC variability	Potential GSK3640254 QD MAD Doses			
%CVb[1]	40mg	80mg	150mg	300mg
0.15	0	0	0	0.009
0.25	0	0	0	0.162
0.35	0	0	0	0.41
0.5	0	0	0.041	0.631

Note: 1, %CVb: between-participant coefficient of variation

5.5.5. Dose Escalation Committee

This study will utilize a dose escalation committee made up of at least the following GSK/VH staff: PI, Sub-Investigator, Medical Monitor, pharmacokineticist, data manager, statistician, and study manager. The committee will evaluate data including but not limited to: AEs, vital signs, laboratory findings, ECG parameters, and PK data. The blinding of personnel is discussed in Section 7.4.

5.5.6. Anticipated Exposure and Safety Cover for a Range of Potential Doses

Projected steady-state exposures of GSK3640254 from potential doses in Part 2, taking into consideration the PK emerging from single doses of 1, 3 and 10 mg, are compared to target efficacious concentrations and preclinical toxicity exposures in Table 8. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats and only to a LOAEL in dogs. Findings in both species were GI related, limited and reversible (see Section 3.3.1 and the CIB for details).

Importantly, the doses listed here are nominal and are intended to demonstrate general concepts relating to factors of escalation. Dose escalation is exposure-based and the specific doses in the SAD and MAD portions are subject to change based upon emerging clinical and PK data gathered in this study. As described above, dose escalations will be governed in real-time by safety and PK. A dose which has met formal clinical, QT, or PK stopping criteria (see Section 8) will not be repeated in the SAD or MAD.

Table 8 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

Parameter	40 mg	80 mg	150 mg	300 mg
Ctrough, ug/mL				
Mean	0.136	0.272	0.509	1.019
Lower bound of 90% CI	0.0680	0.136	0.255	0.510
Ctrough/Ctarget				
Mean	1.23	2.47	4.63	9.26
Lower bound of 90% CI	0.618	1.24	2.32	4.64
Cmax Day 1, ug/mL				
Mean	0.157	0.314	0.588	1.18
Upper bound of 80% CI	0.360	0.720	1.35	2.70
Cmax Cover with				
Rat NOAEL	6.59	3.293	1.756	0.878
Dog LOAEL	11.56	5.780	3.083	1.541
Cmax Day 14, ug/mL				
Mean	0.311	0.622	1.17	2.33
Upper bound of 80% CI	0.484	0.968	1.82	3.63
Cmax Cover with				
Rat NOAEL	4.90	2.448	1.306	0.653
Dog LOAEL	8.60	4.298	2.292	1.146
Mean AUC, ug.h/mL				
Mean	5.09	10.2	19.1	38.17
Upper bound of 80% CI	7.26	14.5	27.2	54.49
AUC Cover with				
Rat NOAEL	3.08	1.542	0.822	0.411
Rat LOAEL	8.41	4.205	2.243	1.12
Dog LOAEL	10.09	5.04	2.69	1.35

Note: The upper bound of the 80% CI is presented to capture the likely highest PK values in 6 subjects. The Cmax and AUC cover were computed as the ratio of Cmax or AUC in animal divided by the Upper Bound of the 80% CI predicted for humans. Ctarget = 3xPBA-EC_{90} (0.11 µg/mL). These predictions are taking into consideration the emerging PK observed after single administration of 1, 3 and 10 mg.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history and psychiatric history, physical examination, laboratory tests, and 24 h Holter monitoring.

Weight

3. Body weight ≥ 50.0kg (110lbs.) for men and ≥ 45.0kg (99lbs) for women and body mass index (BMI) within the range 18.5-32.0kg/m^2 (inclusive).

Sex

4. Male or female

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 14 weeks following the last dose, corresponding to the time needed to eliminate study treatment for potential genotoxic and teratogenic study treatments ***plus*** an additional 90 days (spermatogenesis cycle). In addition, male participants must refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities.
4. Pre-existing clinically relevant, in the opinion of the PI, gastro-intestinal pathology or diagnosis – e.g. irritable bowel syndrome, inflammatory bowel disease, and/or significant baseline signs and symptoms.
5. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
6. Any known or suspected pre-existing psychiatric condition
7. Any positive (abnormal) response confirmed by the investigator on a screening clinician (or qualified designee) administered CSSRS for either the SAD or MAD.
8. Any other clinical condition (including but not limited to active substance use) or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study; unable to comply with dosing requirements; or unable to comply with study visits; or a condition that could affect the absorption, distribution, metabolism or excretion of the drug.

Prior/Concomitant Therapy and Dietary Restriction

9. Unable to refrain from the use of prescription or non-prescription drugs (with the exception of paracetamol), including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and for the duration of the study, unless in the opinion of the Investigator and VH Sponsor and Medical Monitor, the medication will not interfere with the study medications, procedures, or compromise participant safety (see Section 7.7).
10. Unwillingness to abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos within 7 days prior to the first dose of study treatment(s) or until the end of the study.

Prior/Concurrent Clinical Study Experience

11. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
12. Where participation in the study would result in donation of blood or blood products in excess of 500mL within 56 days.

Diagnostic assessments

13. Presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
14. A positive pre-study drug/alcohol screen.
15. A positive test for a diagnostic HIV-1 PCR
16. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
17. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<45 or >100bpm	<50 or >100bpm
PR Interval	<120 or >220msec	
QRS duration	<70 or >120msec	
QTcF interval	>450msec	

Note: A heart rate from 100 to 110bpm can be rechecked by ECG or vitals within 30 minutes to verify eligibility.

18. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).
19. Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
20. Sinus Pauses >3 seconds.
21. Any significant arrhythmia which, in the opinion of the Investigator OR GSK/ViiV Medical monitor, will interfere with the safety for the individual participant.
22. Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).

Other Exclusions

23. History of regular alcohol consumption within 6 months of the study defined as: an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
24. Regular use of tobacco- or nicotine-containing products within 3 months prior to screening.
25. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or their fruit juices from 7 days before the start of study treatment until after the final PK sample in the study.
- Unless otherwise indicated, all doses of GSK3640254 in this study will be administered in the fed state. The participants will fast for approximately 9.5 hours prior to dosing and will receive the moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours post-dose. The moderate fat meal will contain about 600 calories with approximately 30% of them coming from fat.
- For food effect studies, water restrictions may be needed. No water is allowed from 2 hours prior to dosing until 2 hours after dosing except for the glass of water needed to administer the study medication (e.g. 240 mL). Water is allowed ad libitum at all other times.
- For the participants who may receive the study medication in fasted conditions, the participant will fast overnight (for at least 10 hours prior to dosing) and for an additional 4 hours after dosing.
- A snack and meal will be provided 4 hours and 10 hours, respectively, after dosing.
- Meals on Day -1 will follow the Day 1 schedule.

6.3.2. Drugs, Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before admission to the unit (Day-2) until after collection of the final PK sample in each dosing session. Participants will be allowed to have caffeine or xanthine-containing products between dosing periods.
- During each dosing session, participants will abstain from alcohol for 24 hours before admission to the unit (Day-2) until after collection of the final PK sample in each dosing session. Participants will be allowed to have alcohol products between dosing periods up to less than 14 units per week.
- Use of tobacco products will not be allowed from screening until after the final follow-up visit.
- Subjects must have a negative drug test at screening and must abstain from recreational drug use from screening until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. However, reserve participants only need to undergo the screening process once every 90 days; additionally, reserve participants will still be subject to Day -2 and -1 evaluations in routine fashion (as shown in the **SoA** table). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria that established screen failure, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK3640254	Placebo
Dosage formulation:	capsule	capsule
Unit dose strength(s):	1mg, 10mg, 100mg	placebo
Route of Administration	oral	oral
Dosing instructions:	Study medication will be administered by the study personnel during each dosing day with approximately 240 mL of water	Study medication will be administered by the study personnel during each dosing day with approximately 240 mL of water
Packaging and Labelling	Study Treatment will be provided in HDPE bottles. Each bottle will be labelled as required per country requirement.	Study Treatment will be provided in HDPE bottles. Each bottle will be labelled as required per country requirement.
Manufacturer	GSK, Harlow, UK	GSK, Harlow, UK

7.2. Dose Modification

The decision to proceed to the next dose level in both Part 1 (SAD) and Part 2 (MAD) will be made by the VH/GSK study team and study investigator based on safety, tolerability, and preliminary PK data obtained from the prior dose level(s).

7.3. Method of Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedules generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Each subject scheduled to receive study drug will receive a treatment allocation number when randomized. Study treatment will be dispensed at the study visits summarized in (**SoA**).

7.4. Blinding

This will be a double-blind study with participants and the site staff blinded. The sponsor will be unblinded (meaning those staff may have access to unblinded data). For dose escalation, the VH/GSK study team physicians, statistician, and clinical pharmacokinetic staff will have access to unblinded data and present data at dose escalation meetings in a blinded fashion when interacting with site staff. Other VH/GSK staff will remain blinded unless unblinding becomes necessary. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The VH/GSK study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the VH/GSK study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

Participants will be randomized in a 3:1 ratio to receive study treatment (active drug:placebo) within a period or cohort. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study.

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

A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

- Participants will be dosed at the site and they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study or is needed to ensure the participant's safety.

Paracetamol, at doses of ≤ 2 grams/day, is permitted for use at any time during the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from VH/GSK, or with GSK3640254, after the completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

A participant will be withdrawn from the study at any time:

- At his or her own request
- At the discretion of the Investigator or the Sponsor for safety (including lab abnormalities or intercurrent illness), psychiatric, compliance, or administrative reasons.
- Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS during the on-treatment phase (MAD only)
- Any SAE.
- Termination of the study by GSK/VH. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.
- Loss of ability to freely provide consent due to treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding by the PI for any reason
- Repeat non-adherence by the participant with the requirements of the protocol or treatment (as determined by Investigator in consultation with the Medical Monitor)

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If a participant withdraws from the study, he/she must complete a follow-up visit.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant has an ALT ≥3xULN or if the investigator believes that it is in the best interest of the participant.

Details of liver safety follow-up procedures are described in Appendix 7.

8.1.2. QTc Stopping Criteria for Individual Participants

- The Fridericia QT correction formula (QTcF) *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.
- A participant that meets either bulleted criterion below will be withdrawn from the study.
    - QTcF > 500msec,
    - Change from baseline: QTcF >60msec

See the **SoA** for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. PK Stopping Criteria for SAD and MAD

In the SAD, the PK stopping criterion is Cmax 7.96 µg/ml. This is based on the maximum concentration associated with minimal QT effects observed in one dog administered a single dose of 17 mg/kg GSK3640254 (7.96 ug/mL). If safety or PK stopping criteria are not met for the current/prior doses, dose escalation in Part 1 (SAD) will be stopped in the event that the Bayesian predicted probability is >50% that any participant's Cmax for the next subsequent dose will exceed 7.96 µg/mL (the SAD PK stopping criteria).

In the MAD, the PK stopping criterion is AUC 61.1 µg.hr/mL. This is based on the LOAEL exposure (AUC = 61.1 ug.hr/mL) in the rat at 30 mg/kg. At the LOAEL in the rat, microscopic changes in the stomach of rats were observed. These changes were minimal and reversible following 4 weeks of dosing. The rat LOAEL AUC is slightly lower than the mean AUC observed in dogs at the LOAEL dose of 1 mg/kg/day (73.3 µg.h/mL) where microscopic changes in the stomach were observed, and is approximately 3-fold higher than the AUC in rats at the NOAEL dose of 10 mg/kg/day. Dose escalation in Part 2 (MAD) will be stopped in the event that safety or PK stopping criteria are not met, but the Bayesian predicted probability is >50% that any participant's AUC(0-τ) on Day 14 in the subsequent dose will exceed the MAD PK stopping criteria.

8.1.4. Clinical criteria for Stopping the Study

The planned dose escalation within study will be stopped (no new enrollments or further administration of study drug) in the event of any one of the following. However, if any of the criteria are met, an optional cohort may be introduced to assess a lower tolerated dose.

- Two participants within the same Period (SAD) or Cohort (MAD) experience an AE of Grade 3 intensity assessed as related to GSK3640254, by the PI

- One participant experiences an AE of Grade 4 intensity assessed as related to GSK3640254, by the PI
- If greater than 25% of participants within the same Period (SAD) or Cohort (MAD) receiving GSK3640254 have a ≥ Grade 3 intensity AE or lab abnormality (with the exception of asymptomatic changes in lipid panel) or a ≥ Grade 2 intensity rash with concurrent fever, transaminase elevation or eosinophilia.
- There is one Serious Adverse Event (SAE) or death assessed as related to GSK3640254, by the PI.
- 2 participants with confirmed QTcF ≥500 msec within the same Period (SAD) or Cohort (MAD)
- 2 participants with clinically significant, in the opinion of the PI, arrhythmias within the same Period (SAD) or Cohort (MAD)

Finally, if a sentinel participant receiving GSK3640254 meets any of these clinical stopping criteria (G3 or G4 drug-related AE; a drug-related SAE or death; or a G2 rash with concurrent fever, transaminase elevation or eosinophilia), the rest of the Period (SAD) or Cohort (MAD) will not dose and further dose escalation will not occur (see Section 5.1). Of note, the intensity of AEs will be determined using DAIDS criteria (see Section 12.4 for further details)

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge is not allowed. Refer to Appendix 3 for full guidance.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons as described in detail in Section 8.1.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the **SoA** for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she must complete a follow-up visit.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the **SoA**.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns will be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the **SoA**, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the **SoA**.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Time window allowances for all study assessments will be followed according to the time window allowances as indicated in the SRM.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4. As described in Appendix 4, intensity of AEs (and lab abnormalities) will be graded using the DAIDS Grading table. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later clinical trials (Phase 2a and beyond); additionally, the DAIDS criteria are have a more conservative grading scale relative to others (eg. CTCAE v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the **SoA** (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the **SoA** (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority,

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until through the end of pregnancy (termination or delivery).
- If a pregnancy is reported, the investigator will inform GSK within 24 hours of learning of the pregnancy and will follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of GSK3640254 greater than a planned dose level within a 20-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the investigator will:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3640254 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis immediately and through 7 days if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the **SoA**.

9.4.1. Physical Examinations

- Consider further specifications (eg, for height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes) if appropriate for the study.
- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

9.4.3. Electrocardiograms

9.4.3.1. 12-lead safety ECGs

Safety ECGs will be printed and interpreted on-site by the Investigator to ensure subject safety. Safety ECGs may be printed from the Global Instrumentation Holter device (see below). ECG parameters from safety ECGs will not be collected unless as part of an observed adverse events (e.g. 1st degree AV block with PR 240 msec). Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.3.2. Cardiodynamic assessment (ECGs extracted from Holter recordings)

The frequency of ECG data in the SAD and MAD arises from emerging literature suggesting frequent QT evaluation early in development may mitigate the need for a formal TQT study (Darpo, 2014). ECGs will be extracted as shown in the SOA from the SAD and the MAD component of the study, not including the extension cohort. Should clinical development of GSK3640254 continue, an exploratory objective of this study is

to assess the exposure-response relationship between GSK3640254 and QTcF following single and repeat dose administration.

The 12-lead Holter and ECG equipment will be supplied and supported by iCardiac Technologies, Inc. All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses will be selected at pre-determined time points as defined in the SOA, and will be read centrally by iCardiac Technologies, Inc.

The following principles will be followed in iCardiac's core laboratory:

- ECG analysts are blinded to the participant, visit and treatment allocation
- Baseline and on-treatment ECGs for a particular participant will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead is lead II. If lead II is not analyzable in any specific participants, then primary lead of analysis will be changed to another lead for the entire participant data set.

The following is a brief description of ECG analysis methods utilized by iCardiac' core laboratory.

TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by iCardiac Technologies. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (e.g., the HR and QT changes from beat-to-beat in the range of <10%). At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

High-Precision QT Analysis

High-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" is performed using COMPAS software. All low confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from

each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

Categorical T-wave morphology analysis (Table 9) and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

Table 9 T-wave morphology categories (assessed manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the **SoA** for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 days after the last dose of study treatment will be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology will be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4.5. Suicidal Risk Monitoring

GSK3640254 is not a CNS active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the CSSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator, will exclude them from participating. Finally, participants in the MAD will have assessment by the CSSRS during the on-treatment phase of the study (see SoA table for details). As described in Section 8.1, any positive (abnormal) response confirmed by the investigator during the on-treatment phase will result in their discontinuation. In either case (screening or on-treatment) of positive (abnormal) response confirmed by the investigator, the PI/SI will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment.

9.4.6. GI Toxicity Evaluation and Monitoring Plan

Pre-clinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254. This section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table 10). The Investigator may contact the GSK/VH Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table 10 GI Toxicity Evaluation and Management

HISTORY	For symptoms of all grades, a thorough history forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical trial.
Nausea and Vomiting	The investigator should attempt to identify the etiology of these symptoms (and whether it is intraperitoneal, extraperitoneal, medication related, infection related, or due to a metabolic disorder (Hasler, 2012). Medications can cause nausea and vomiting acutely.
Dyspepsia	The Investigator should identify the presence of red flags (odynophagia, unexplained weight loss, recurrent vomiting, GI bleeding, jaundice, palpable mass or adenopathy, or family history of GI malignancy). Symptoms of dyspepsia could include early satiety, bloating, or belching. Additionally, atypical symptoms of dyspepsia could include: pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical trial are available elsewhere (Rome Foundation, 2014).
PHYSICAL EXAMINATION	Physical examination should complement elements obtained from the history (Hasler, 2012). Acutely, the investigator may assess for signs of intravascular volume depletion (eg, orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (eg, from an ulcer). Complete evaluation of dyspepsia should include an oral examination (poor dentition or pharyngeal erythema) and lungs for wheezing.
DIAGNOSTIC EVALUATION AND MANAGEMENT	A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; Investigators should exercise good clinical judgment in this regard (Soll, 2009). A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities. Consultation (eg, gastroenterologist) is recommended as clinically indicated.

Grade 1 symptoms	Participants may be treated symptomatically. If participants develop dyspepsia alone, generally only limited and direct diagnostic testing should be performed. If the participant has dyspepsia they should limit alcohol, caffeine, chocolate, tobacco, and eating directly before bedtime.
Grade 2 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): Serum chemistries and assessment of hemoglobin if not recently performed. Testing for Helicobacter pylori PCR for viruses (eg, CMV) For participants who are infected with H. pylori discontinuation from the trial is necessary. Management should be targeted at addressing the underlying pathology.
Grade 3 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • CT scan to identify gastrointestinal inflammation • Upper endoscopy with biopsy as indicated (eg, mucosal injury or the presence of red flags). Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms[a]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 and Grade 3 • An acute abdominal series Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

a. For Grade 3-4 GI AEs related to active drug: the Investigator should consider discontinuing the partcipant from the study and performing an evaluation/management plan incorporating elements above.

9.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the **SoA**. An additional 2 mL of whole blood samples will be collected for metabolite profiling at the same time points as the PK samples on Day 1, Day 2, Day 14 and Day 15, in MAD cohorts 3, 4, 5 and 6, as specified in the **SoA**. A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Urine samples will be collected for 24 hours on Day 1 and Day 14 in MAD cohorts 3, 4, 5 and 6 for measurement of urine concentrations of GSK3640254 as specified in the **SoA**.
- The metabolite profiling of the plasma and urine samples will be conducted under separate protocols and results are reported separately according to the protocols.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

A 10-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study for the MAD portion of the study only. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

No formal statistical hypotheses are to be tested. Sample size is based on feasibility. No formal calculation of power or sample size for Parts 1 and 2 of the study has been performed. A sample size of approximately 8 participants per dose-cohort should be sufficient to provide useful estimates of both inter- and intra-participant variability for GSK3640254 PK parameters, and initial safety assessment.

As described in Section 5.1, an expansion cohort is included in this study in order to evaluate the rate of GI intolerability. No formal statistical testing will be performed. However, based on prior information from GSK3532795 studies, a conservative clinical estimate of GI AEs in those receiving placebo would be 10%; a sample size of 24 participants on active and 14 participants on placebo would have 90% power to detect a 45% difference between placebo and GSK3640254.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All enrolled participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic Concentration	The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.
Pharmacokinetic Parameter	The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.

10.3. Statistical Analyses

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population and details will be provided in the Reporting and Analysis Plan (RAP).

Endpoint	Statistical Analysis Methods
Primary	Safety data will be presented in tabular and or graphic format and summarized descriptively accordingly to GSK's Integrated Data Standards Library (IDSL) standards
Exploratory	Will be described in the reporting and analysis plan

AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product. AEs leading to withdrawal will also be summarized by treatment.

10.3.2. Other Analyses

PK and safety response exploratory analyses will be described in the reporting and analysis plan. The population PK analysis and safety response analyses may be presented separately from the main clinical study report (CSR).

Pharmacokinetic Analyses

Plasma GSK3640254 concentration-time data will be analyzed by noncompartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. Individual plasma PK parameters for each participant and dosing group will be determined, including:

- Part 1 (single dose): AUC (0-24), AUC(0-tlast), AUC (0-inf), Cmax, C24, tmax, tlag, t1/2, Clast, tlast, CL/F.
- Part 2 (Repeated QD doses for 14 days):
    - Day 1: AUC(0-24), Cmax, C24, tmax, tlag
    - Day 14: AUC(0-τ), Cmax, Cτ, tmax, t1/2, and CL/F.

Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK.

Plasma GSK3640254 concentrations and PK data will be summarized by treatment and listed by participant. Unless stated otherwise, descriptive summaries will include number (n), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum for continuous variables, n and percent (%) for categorical variables, and geometric mean, 95% confidence interval (CI), and the between-participant CV (%CVb) for the log-transformed PK parameters.

Dose proportionality of selected single and repeated dose PK parameters will be assessed by the power model.

Accumulation will also be evaluated for each treatment by determining the ratio of Day 14 (Part 2) to Day 1 AUC(0-τ) (R(AUC(0-τ)), Cmax (R(Cmax)), and Cτ (R(Cτ)). C24 on Day 1 will be taken as the Cτ on that day.

Attainment of steady-state will be assessed by estimating the slope of pre-dose concentrations for GSK3640254 on Days 2-14 (Part 2). The final assessment of the slope will be determined by at least the last 3 pre-dose concentrations.

For the assessment of food effect (if conducted), the $\log_e$-transformed PK parameters will be separately analyzed using a mixed effect model with a fixed effect term for fed vs. fasted. Participant will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals CIs will be calculated for the difference in PK parameter values for the 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, fed/fasted in PK parameter values on the original scale.

The details of the statistical analysis of PK data will be described in the RAP.

Pharmacokinetic/Safety Response Analyses

Pharmacokinetics/Safety Response analyses will be performed only if the GSK3640254 development project is progressing forward. The endpoint for the potential impact of GSK3640254 on cardiac repolarization will be the change-from-baseline QTcF (ΔQTc). A modelling approach will be used to describe the relationship between GSK3640254 concentration and QTc data.

The details of the PK/Safety Response analysis will be described in the RAP or in a separate analysis plan if the analysis is reported separately.

10.3.3. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available pharmacokinetic data will be reviewed internally at VH/GSK prior to each dose escalation or administration. Safety data (labs, vital signs, ECG, AEs, SAEs) will be reviewed by the PI/Sub-I and VH/GSK study team after completion of each dose level. Dose escalation can only occur after PI/Sub-I and VH/GSK study team has found that the safety, PK profiles are supportive to proceed with the evaluation of the next higher dose level (See Section 5.5.5 Dose Escalation Committee).

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.

$$y_{ij} = \theta_1 + \theta_2 d_{ij} + s_i + \epsilon_{ij} \quad [1]$$

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 ii-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.

$$y_i = \theta_1 + \theta_2 d_i + \epsilon_i \quad [2]$$

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.

Bayesian model Operating Characteristics (OC)

In this part, we want to explore the operating characteristics of the 700mg dose for SAD. Given different assumptions of with-in and between participant Cmax variability (CV%), and assuming dose proportionality (slope=1), data for 1000 trials were simulated based on Whitehead's model [1]. Each simulated trial contains Cmax values for 6 subjects on treatment for doses ranging from 1mg to 400mg in SAD cohort 1 and cohort 2.

For each simulate trial, we fitted the mixed effect Bayesian model based on mode [1]. In the following procedure, we calculated the Bayesian probability of an individual exceeding the Cmax threshold:

We had 10000 iterations in the MCMC procedure. In each iteration, we obtained the estimated parameters $\hat{\theta}_1, \hat{\theta}_2, \hat{s}_i (i = 1,2, \ldots, 6)$ and $\hat{\sigma}^2$(the estimated standard deviation of ϵ_{ij}), Based on the estimation, a random sample for each subject, which represented the simulated exposure in the 700mg dose, was drawn from the distribution $N(\hat{\theta}_1 + \hat{\theta}_2 \cdot 200 + \hat{s}_i, \hat{\sigma}^2)$. We counted the number of iterations N with any simulated exposure exceeding the Cmax threshold log(7.96). The Bayesian probability was calculated as $1 - \frac{N}{10000}$.

For each trial, the Bayesian probability for the 700mg dose is calculated and compared with different thresholds (40%, 50% or 60%). Among those 1000 trials, the percentages

of trials with Bayesian probability below the thresholds, which stands for the percentage of trials that could be escalated to dose 700mg, are listed in Table 11.

Table 11 Percentage of trials with Bayesian probability less than the threshold (40%, 50% or 60%)

Cmax Variability		Probability Threshold		
%CVw[1]	%CVb[1]	40%	50%	60%
7.5	15	100.0%	100.0%	100.0%
15	15	100.0%	100.0%	100.0%
12.5	25	99.9%	100.0%	100.0%
25	25	99.3%	99.5%	99.8%
17.5	35	95.6%	97.0%	98.5%
35	35	91.0%	94.0%	97.1%
25	50	75.7%	81.9%	85.2%
50	50	53.9%	66.8%	77.0%

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

Based on the table above, when with-in and between participant Cmax variability are small or moderate, the probability of successfully escalating to 700mg is high.

10.3.4. Final Analyses

Final analysis will be performed after the completion of the study and final datasets authorization.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by participant, treatment and day; summaries will be presented by treatment, day, and time for each part.

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-participant CV (%CVb) for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ARV	Anti-retroviral
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)
AUC(0-24)	Area under the plasma concentration time curve from zero to 24
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-tlast)	Area under the concentration-time curve from zero to time of last sample taken
BID	Twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
cART	Combination anti-retroviral therapy
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CL/F	Apparent oral clearance
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CSSRS	Columbia Suicide Severity Rating Scale

CV	Cardiovascular
CVb	Between-participant coefficient of variation
ECG	Electrocardiogram
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FTIH	First-time-in-human
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIV-1	Human immunodeficiency virus-1
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LOAEL	Lowest observed adverse effect level
MAD	Multiple ascending dose
MI	Maturation inhibitors
MOA	Mechanisms of action
MSDS	Material Safety Data Sheet
NOAEL	No observed adverse effect level
OC	Operating Characteristics
PBO	Placebo
PCR	Polymerase chain reaction

PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
POC	Proof of Concept
RAP	Reporting and Analysis Plan
SAD	Single ascending dose
SAE	Serious Adverse Event
SD	Standard deviation
SOA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
VH	ViiV Healthcare
WOCBP	Women of Childbearing Potential

Trademark Information

Trademarks owned by the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
DAIDS
Phoenix
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium, Chloride, Bicarb	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium, Magnesium, Phosphate	Alkaline phosphatase	Fasting Lipid Panel (Cholesterol, Triglycerides, HDL, LDL)
Routine Urinalysis	• Specific gravity			

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Breath alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed)[2]Serology and PCR [(HIV-1 diagnostic PCR, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] The results of each test must be entered into the CRF.

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded or the subject has undergone emergency unblinding.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Furthermore, a substantial amendment will require approval from the MHRA before implementation.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committee Structure

This study will utilize a dose escalation committee made up of the at least the following GSK/VH staff: Principle Investigator, Sub-Investigator, Medical Monitor, pharmacokineticist, data manager, statistician, and study manager. The committee will evaluate data including but not limited to: AEs, vital signs, laboratory findings, ECG parameters, and PK data.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Study Reference Manual (SRM).

Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent

one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the DAIDS grading table (http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf) and assign it to 1 of the following categories:

- Mild: no or minimal interference with usual social & functional activities
- Moderate: greater than minimal interference with usual social & functional activities
- Severe: inability to perform usual social & functional activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- Life Threatening: inability to perform basic self-care functions

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- Refrain from donating sperm for duration of study and for 14 weeks after study completion or from last dose.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 38 days after the last dose of study treatment

Pregnancy Testing

- Additional pregnancy testing should be performed at screening (both SAD and MAD) and prior to dosing in each period (SAD only) during the treatment period and at 37 days after the last dose of study treatment and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact an MAD participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to study treatment and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to study treatment. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed for clinical correlation related to study treatment. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment (or study treatments of this class) continues but no longer than 5 years or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

The procedures listed below are to be followed if a participant meets the liver chemistry stopping criteria defined in Section 8.1.1:

- Immediately withdraw the participant from study treatment
- Notify the VH/GSK medical monitor within 24 hours of learning of the abnormality to confirm the participant's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Appendix 4), the SAE data collection tool will be completed separately with the relevant details.

Safety Follow-Up Procedures for participants with ALT ≥ 3x ULN:

- Monitor participants weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for participants with ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin); or ALT ≥ 3x ULN and INR1 > 1.5:

- This event is considered an SAE (see Appendix 4). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have participants return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for all participants with ALT ≥ 3x ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including: Hepatitis A IgM antibody, Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM), Hepatitis C RNA, Cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 48 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for participants with ALT ≥ 3x ULN and bilirubin ≥ 2x ULN (>35% direct) but are optional for other abnormal liver chemistries:

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

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment: 01; 12-JUL-2017

Overall Rationale for the Amendment: This amendment makes three changes to the protocol. First, the 24 h Holter Monitor at Day -2 in SAD and MAD has been removed. Second, language in the MAD Schedule of Analyses table, Footnote 1 changed from Holter to Continuous ECG. Finally, the protocol serum alcohol and drug screen has been changed to: 1) breath alcohol and 2) urine drug screen.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Removed 24 h Holter Monitor at Day -2 in SAD and MAD	Since study participants will already have a Holter completed during screening, this amendment has removed the 24 h Holter Monitor at Day -2. This change does not affect the risk benefit ratio to participants.
Section 2 Schedule of Activities	Changed MAD Schedule of Analyses table Footnote 1 from Holter to Continuous ECG	This change in language reflects the use of the term Continuous ECG in the Schedule of Analysis table. This change does not affect the risk benefit ratio to participants.
Section 12.2 Clinical Laboratory Tests	Changed Serum alcohol and drug screen to: 1) breath alcohol and 2) urine drug screen	This change allows for improved participant convenience in the trial while still maintaining robust exclusion criteria. This change does not affect the risk benefit ratio to participants.

Amendment: 02; 3-AUG-2017

List of Specific Changes

Section # and Name	Description of Change	Brief Rationale
Synopsis	Figure 1 footnote removed and reference to a dose of 400 mg was removed.	Figure 1 footnote removed and reference to a dose of 400 mg was removed. This change further addresses risk to

Section # and Name	Description of Change	Brief Rationale
		participants.
Section 2 Schedule of Analyses	The components of a Full Physical Exam are described to include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Additionally, full physical exams now replace brief physical exams.	To address the risk for neuropsychiatric events, a neurological evaluation will occur during scheduled full physical exams. This change further addresses risk to participants.
Section 2 Schedule of Analyses	A clinician (or qualified designee) administered CSSRS assessment has been added to the screening evaluation (SAD and MAD) and in the on-treatment phase of the MAD portion.	To address the risk of suicidal ideation identified with a similar asset, all participants will be screened with a clinician (or qualified designee) administered CSSRS. Additionally, the MAD portion of the trial will include use of the CSSRS during the on-treatment phase. This change further addresses risk to participants.
Section 2 Schedule of Analyses	The fasting lipid panel is now separate from the routine chemistry panel.	The fasting lipid panel is now separate from the routine chemistry panel. This change does not affect the risk benefit ratio to participants.
Section 3.3 Benefit Risk Assessment	A clinician (or qualified designee) administered CSSRS assessment has been added to the screening evaluation for the entire study (SAD and MAD) and the on-treatment phase of the MAD portion	To address the risk of suicidal ideation identified with previous MI GSK3532795, the MAD portion of the trial will include use of the CSSRS during the on-treatment phase. Also, the entire trial (SAD and MAD) will exclude any subject who has a positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered CSSRS at screening. These changes further address risk to

Section # and Name	Description of Change	Brief Rationale
		participants.
Synopsis- Overall Design and Section 5.1 Overall Design	Reference to a dose of 400 mg was removed. Further clarity added to maximum dose in the SAD.	The anticipated maximum single dose of GSK3640254 in Part 1 will not exceed 6X, where X is the minimally efficacious dose given once daily and assuming 50% accumulation with repeat dosing. This maximum dose would allow exposure coverage of the highest anticipated MAD dose (4X). Based on current assumptions, the maximum dose in Part 1 (SAD) is projected to be 200 mg. These changes further address risk to participants.
Section 5.1	Figure 2 footnote removed and reference to a dose of 400 mg was removed.	Figure 2 footnote removed and reference to a dose of 400 mg was removed. This change further addresses risk to participants.
Section 5.4 Scientific Rationale for Study Design	Statement describing the rationale for the assessment of a therapeutic dose range in healthy subjects was added	To provide justification for assessment of an exposure range in healthy subjects that is anticipated to be the therapeutic exposure range in the target HIV-1-infected population. This change does not affect the risk benefit ratio to participants

Section # and Name	Description of Change	Brief Rationale
Section 5.5.2 Predicted Human Efficacious Dose	Information regarding inhibitory quotient (IQ) has been added.	To provide justification for plans to assess doses up to 4 times the anticipated minimally effective dose in healthy subjects. This change does not affect the risk benefit ratio to participants
Section 5.5.3 Part 1 (SAD) Starting Dose and Dose Escalation	Clarity on the maximum dose in the SAD provided.	The anticipated maximum single dose of GSK3640254 in Part 1 will not exceed 6X, where X is the minimally efficacious dose given once daily and assuming 50% accumulation with repeat dosing. This maximum dose would allow exposure coverage of the highest anticipated MAD dose (4X). Based on current assumptions, the maximum dose in Part 1 (SAD) is projected to be 200 mg.
Section 6.2 Exclusion Criteria	A clinician (or qualified designee) administered CSSRS assessment has been added as a screening evaluation for both the SAD and MAD.	To address the risk of suicidal ideation identified with previous MI GSK3532795, the entire trial (SAD and MAD) will exclude any subject who has a positive (abnormal) response confirmed by the investigator to the CSSRS at screening. This change further addresses risk to participants.
Section 8.1 Discontinuation of Study Treatment	Discontinuation criteria have been clarified to state a participant will be discontinued for any of the events described in this section. Two additional discontinuation criteria have been added: 1) Development of an SAE and 2) Emergence of any positive (abnormal) response confirmed by the investigator on the CSSRS during the on-treatment phase	Emergence of these events now mandate discontinuation from the trial. This change further addresses risk to participants.

Section # and Name	Description of Change	Brief Rationale
	(MAD only)	
Section 9.4.5 Suicidal Risk Monitoring	Clarification of the use of a clinician (or qualified designee) administered CSSRS at screening (all subjects in SAD and MAD) and during the on-treatment portion of the MAD has been added.	To address the risk of suicidal ideation identified with previous MI GSK3532795, the entire trial (SAD and MAD) will exclude any subject who has a positive (abnormal) response confirmed by the investigator to a clinician (or qualified designee) administered CSSRS at screening. The MAD portion of the trial will include use of the CSSRS administered by a clinician (or qualified designee) during the on-treatment phase of the study. A positive (abnormal) response confirmed by the investigator, at screening or on-treatment will result in the participant being excluded from participation (SAD or MAD) or discontinuing the study (MAD only), respectively. Subsequently the PI/SI will arrange for urgent specialist psychiatric evaluation and management. These changes further address risk to participants.
Section 12.3 Study Governance	Clarification made that any substantial amendment will require approval from the MHRA before implementation.	Any substantial amendment to the protocol will require MHRA approval. This change does not affect the risk benefit ratio to participants

Amendment: 03; 5-DEC-2017

Summary of Amendment Changes with Rationale:

The primary purpose of this protocol amendment (03) is to increase the maximum dose in the SAD part of the study from 200 mg to ≤ 700 mg, in relation to human exposure to GSK3640254 being approximately 70% lower than predicted based on animal data. Preliminary PK parameters for GSK3640254 following single dose administration of 1, 3, and 10 mg show exposures that were lower along with a longer half-life than predicted based on animal data. The prediction for a 10 mg dose were a mean Cmax of 197 ng/mL, a mean AUC of 3430 ng.h/mL and a mean half-life of 15 hours. The observed Cmax was approximately 75% lower, the AUC was approximately 65% lower and the half-life was about 70% longer. Taking into consideration the actual human PK profile of GSK3640254 at 1, 3 and 10 mg, the minimally anticipated efficacious dose (X) has increased from 40 mg to 70 mg with an accumulation upon repeated once daily administration increasing from 50% to approximately 115%. In order to evaluate exposure anticipated at the maximum MAD dose of up to 4X, higher doses up to 9X will need to be evaluated in the SAD. Thus, this amendment is to enable the evaluation of the safety/tolerability and pharmacokinetics of single doses of GSK3640254 at doses ≤ 700 mg in healthy volunteers continuing to participate in Cohorts 1 and 2. Specifically, the proposed higher doses will be evaluated in Period 4 (Cohort 1, ≤ 400 mg; Cohort 2, ≤ 700 mg). Other, non-major changes, have also been incorporated.

List of Specific Changes

Section # and Name	Description of Change	Brief Rationale
Title Page	The sponsor was changed back from GSK to VH.	VH is the sponsor of the study.
Sponsor Signatory Page	The Signatory was changed back from Harmony Garges to Max Lataillade.	Max Lataillade is the Sponsor.
Overall Design	The Doses for SAD, Period 4 (Cohorts 1 and 2) were increase from 200 mg to ≤ 400 and ≤ 700 mg, respectively in Figure 1.	This is based upon a need to increase doses to attain the prior desired exposures. Preliminary review shows (dose proportional) exposures that have been approximately 70% lower than anticipated after single doses of 1, 3, and 10 mg.
Section 2 SAD **SoA** Table	The Full PE can be performed on D-2 or D-1. A BMI does not need to be measured on D-1.	This flexibility improves the subject experience in the clinical trial without clinical or scientific consequence.
Section 2 MAD SoA table	Only urine metabolite sampling will be performed. Next, plasma PK, plasma metabolite, and urine metabolite sampling will be determined by SRM time window allowances. The Full PE can be performed on D-2 or D-1. A BMI does not need to be measured on D-1. A PGx sample will be drawn on D-1.	The SRM has been updated to reflect the time windows needed for accurate sampling. This flexibility improves the subject experience in the clinical trial without clinical or scientific consequence.
Section 3.2.2 Preliminary Safety and PK data in Current Study (SAD doses 1, 3, and 10 mg)	A new section summarizing preliminary safety/PK data for 1, 3, and 10 mg SAD doses was added.	A new section needed to be added to describe emerging data.
Section 5.1 Overall Design	The Doses for SAD, Period 4 (Cohorts 1 and 2) were increase from 200 mg to ≤ 400 and ≤ 700 mg,	This is based upon a need to increase doses to attain the prior desired exposures. Preliminary review shows

Section # and Name	Description of Change	Brief Rationale
	respectively in Figure 2.	exposures that have been approximately 70% lower than anticipated after single doses of 1, 3, and 10 mg.
Sections 5.5.1 – 5.5.4 Predicted Human PK Predicted Human Effective Dose Part 1 and 2 Starting Dose and Dose Escalation	References to predicted human PK are changed to past tense and preliminary single dose data from 1, 3, and 10 mg are inserted. Projections for PK in the SAD and MAD have been re-calculated. MAD dose escalation will not exceed approximately 2 fold.	Preliminary review shows (dose proportional) exposures that have been approximately 70% lower than anticipated after single doses of 1, 3, and 10 mg. Thus, the PK parameters were re-estimated. Dose escalation by approximately 2 fold in the MAD will minimize the pill burden encountered by participants taking study medication for 14 days.
Section 5.5.6 Anticipated Exposure and Safety Cover for a Range of Potential Doses	Projections for steady state PK were re-calculated based upon preliminary single dose data from the 1, 3, and 10 mg dose arms.	Preliminary review shows exposures that have been approximately 70% lower than anticipated after single doses of 1, 3, and 10 mg. Thus, the steady state PK was re-estimated
Section 6.4 Screen Failures	Text clarified to state reserve participants need to be screened once every 90 days These reserve participants still need to undergo evaluations on D-2 and D-1 as per the **SoA** table.	This additional text prevents reserve participants from undergoing excessive rescreening evaluations during the study.
Section 9 Study Assessments and Procedures	Time allowances for the study assessments will be followed according to the SRM.	The SRM has been updated to reflect the time windows needed for accurate evaluations.
Section 9.5 Pharmacokinetics	Removal of urine PK profiling text.	Existing text, combined with the SRM, is sufficient for existing sampling.
Section 10.3.3 Bayesian Model Operating	The Bayesian Model was re-calculated using a max single	The probability of successful escalation to a 700 mg single dose is needed if doses are to

Section # and Name	Description of Change	Brief Rationale
Characteristics	dose of 700 mg.	increase as proposed.
Section 12.8 Appendix 8	The information from Amendment 2 was placed in this section.	Amendment 2 was previously approved.

Sponsor Name:

PREVIOUS TEXT

GlaxoSmithKline Research & Development Limited

REVISED TEXT

~~GlaxoSmithKline Research & Development Limited~~

ViiV Healthcare UK Limited

Sponsor Signatory:

PREVIOUS TEXT

Harmony P. Garges, MD

Global Medical Sciences

ViiV Healthcare

REVISED TEXT

~~Harmony P. Garges, MD~~

~~Global Medical Sciences~~

~~ViiV Healthcare~~

Max Lataillade, DO, MPH

VP, Clinical Development

ViiV Healthcare

Revision Chronology

PREVIOUS TEXT

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	03-AUG-2017
Amendment 01	12-Jul-2017
Original Protocol	25-May-2017

REVISED TEXT

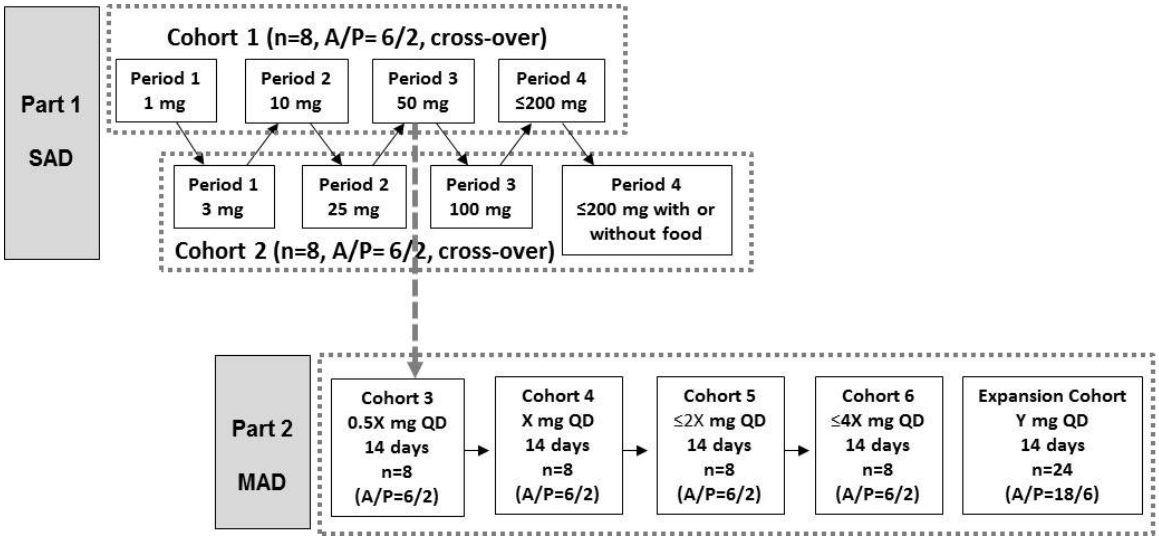
DOCUMENT HISTORY	
Document	**Date**
Amendment 03	**05-Dec-2017**
Amendment 02	03-AUG-2017
Amendment 01	12-Jul-2017
Original Protocol	25-May-2017

1. SYNOPSIS

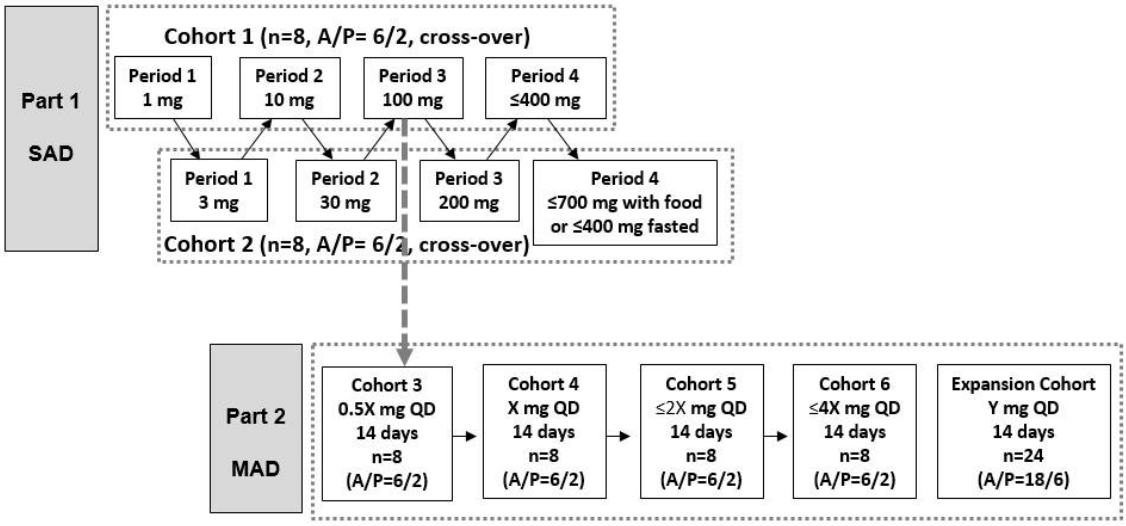
Overall Design

Figure 1 Phase 1 Study in Healthy Participants using planned doses of GSK3640254

PREVIOUS TEXT



REVISED TEXT


Part 1
SAD
Cohort 1 (n=8, A/P= 6/2, cross-over)
Period 1
1 mg
Period 2
10 mg
Period 3
100 mg
Period 4
≤400 mg
Period 1
3 mg
Period 2
30 mg
Period 3
200 mg
Period 4
≤700 mg with food
or ≤400 mg fasted
Cohort 2 (n=8, A/P= 6/2, cross-over)
Part 2
MAD
Cohort 3
0.5X mg QD
14 days
n=8
(A/P=6/2)
Cohort 4
X mg QD
14 days
n=8
(A/P=6/2)
Cohort 5
≤2X mg QD
14 days
n=8
(A/P=6/2)
Cohort 6
≤4X mg QD
14 days
n=8
(A/P=6/2)
Expansion Cohort
Y mg QD
14 days
n=24
(A/P=18/6)

2. SCHEDULE OF ACTIVITIES (SOA):

SAD Cohorts 1 and 2 On-Treatment: Before, During, and After Dosing in Each Period

PREVIOUS TEXT

Procedure	Periods 1 through 4																					Follow-up (7-14 days post last dosing)
	Day -2	Day -1	Day 1															Day 2	Day 3	Day 4	Day 5	
			Pre-dose	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	3.5 h	4 h	4.5 h	5 h	6 h	8 h	12 h	24 h	48 h	72 h	96 h	
Admission to Unit	X																					
Outpatient Visit																						X
Full Physical Exam[1]		X																	X			X
Weight, BMI		X																				
Vital signs		X				X		X					X		X		X	X	X	X	X	X
12-lead safety ECGs	X	X	X			X		X				X			X		X	X	X	X	X	X
Continuous ECG (full time matched baseline on Day-1)[2]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy Test	X																					X[3]
Drug/alcohol/cotinine screen	X																					
Hem/Chem/Urine tests	X																	X	X		X	X
Single Dosing with GSK3640254 following moderate fat meal				X																		
Plasma PK Sampling[4]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	<==========>																					

Con Med Review	<==========																				==========>
Furlough from Unit																				X	

HCV=Hepatitis C; BMI= Body mass index; ECG= Electrocardiogram; PK= Pharmacokinetic, SAD=single ascending dose

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
2. Additional safety ECGs may be printed at the discretion of the PI if prolongation in QT interval is suspected. The frequency of ECGs will support an exploratory endpoint (should clinical development continue) to evaluate the exposure-response relationship between GSK3640254 and QTcF. Once human PK data (e.g. Cmax) are available, the number of ECG time points may be reduced in subsequent dosing groups. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order.
3. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
4. The number of PK sampling time points may be reduced in subsequent dosing groups once human PK data are available.

REVISED TEXT

Procedure	**Periods 1 through 4**																					**Follow-up (7-14 days post last dosing)**
	Day -2	**Day -1**	**Day 1**															**Day 2**	**Day 3**	**Day 4**	**Day 5**	
			Pre-dose	**0 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**2.5 h**	**3 h**	**3.5 h**	**4 h**	**4.5 h**	**5 h**	**6 h**	**8 h**	**12 h**	**24 h**	**48 h**	**72 h**	**96 h**	
Admission to Unit	X																					
Outpatient Visit																						X
Full Physical Exam[1]	**X**	X																	X			X
Weight, BMI[2]		X																				
Vital signs		X				X		X					X		X		X	X	X	X	X	X
12-lead safety ECGs	X	X	X			X		X				X			X		X	X	X	X	X	X

Continuous ECG (full time matched baseline on Day-1)[3 2]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy Test	X																					X[4 3]
Drug/alcohol/cotinine screen	X																					
Hem/Chem/Urine tests	X																	X	X		X	X
Fasting Lipid test	X																				X	X
Single Dosing with GSK3640254 following moderate fat meal				X																		
Plasma PK Sampling[5 4]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	<==========																					==========>
Con Med Review	<==========																					==========>
Furlough from Unit																					X	

HCV=Hepatitis C; BMI= Body mass index; ECG= Electrocardiogram; PK= Pharmacokinetic, SAD=single ascending dose

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. **A single exam can be performed on D-2 or D-1.**
2. **A BMI does not need to be measured at the time of measurement**.

3. Additional safety ECGs may be printed at the discretion of the PI if prolongation in QT interval is suspected. The frequency of ECGs will support an exploratory endpoint (should clinical development continue) to evaluate the exposure-response relationship between GSK3640254 and QTcF. Once human PK data (e.g. Cmax) are available, the number of ECG time points may be reduced in subsequent dosing groups. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order.
4. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
5. The number of PK sampling time points may be reduced in subsequent dosing groups once human PK data are available.

MAD Cohorts 3, 4, 5, 6 and the Expansion Cohort Screening

PREVIOUS TEXT

Procedure	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Follow-up (7-14 days post last dosing)
																0h	24h	48h	72h	96h	
Admission to Unit	X																				
Outpatient Visit																					X
Full Physical Exam[1]		X						X						X			X			X	X
CSSRS						X														X	
Weight, BMI		X																			
Vital signs		X	X	X		X		X		X		X		X		X			X		X
12-lead safety ECGs	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X	X
Continuous ECG (full time matched baseline on Day-1)[2]		X	X	X												X	X				
Drug/alcohol/cotinine screen	X																				
Hem/Chem/Urine tests	X			X		X		X		X		X		X		X		X		X	X
Pregnancy Test	X																				X[3]
QD Dosing with GSK3640254 following moderate fat meal			X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Plasma PK Sampling[4]			X	X	X	X		X		X		X		X		X	X	X	X	X	

Procedure	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Follow-up (7-14 days post last dosing)
																0h	24h	48h	72h	96h	
Plasma Metabolite Sampling[5]			X	X												X	X				
Urine PK and Metabolite Sampling[6]			X	X												X	X				
PGx Sampling (if participant consents)	X																				
Adverse Event Review	<==========>																				
Con Med Review	<==========>																				
Furlough from Unit																				X	

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
2. ECG data extracted from the Continuous ECG will be assessed before PK sampling, prior to dosing and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4.5, 5, 5.5, 6, 8, 12 h, and 24 h post dose on Day 1 and Day 14 and on corresponding timepoints on Day -1. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order. The frequency of EKGs will support an exploratory endpoint to evaluate (should clinical development continue) the ER relationship between GSK3640254 and QTcF. Once human data (eg Cmax) is known, the number of EKG time points may be reduced.
3. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
4. Plasma PK samples for bioanalysis for GSK3640254 will be collected pre-dose (within 15 minutes prior to dosing) and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12 h on Day 1 and Day 14. On dosing days, plasma PK will be collected pre-dose. The number of PK sampling time points may be reduced in the initial MAD cohort as well as further in subsequent MAD dosing groups once human PK data are available in the SAD as well as in the initial MAD cohorts.

5. Plasma Metabolite samples for metabolite identification will be collected pre-dose (within 15 minutes prior to dosing) and at the same time points as for plasma PK samples on Day 1, Day 2 and Day 14, and Day 15. Plasma metabolite samples will not be collected in the expansion cohort.
6. Urine PK and Metabolite Sampling for bioanalysis and metabolite identification will be collected pre-dose (within 1 hour prior to dosing) and from time 0 up to 24 hours on Day 1 and Day 14. Urine samples will not be collected in the expansion cohort.

REVISED TEXT

Procedure	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14** 0h	**Day 15** 24h	**Day 16** 48h	**Day 17** 72h	**Day 18** 96h	**Follow-up (7-14 days post last dosing)**
Admission to Unit	X																				
Outpatient Visit																					X
Full Physical Exam[1]	**X**	X						X						X			X			X	X
CSSRS						X														X	
Weight, BMI[2]		X																			
Vital signs		X	X	X		X		X		X		X		X		X			X		X
12-lead safety ECGs	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X	X
Continuous ECG (full time matched baseline on Day-1)[3] [2]		X	X	X												X	X				
Drug/alcohol/cotinine screen	X																				
Hem/Chem/Urine tests	X			X		X		X		X		X		X		X		X		X	X
Fasting Lipid test	X									X								X			X
Pregnancy Test	X																				X[4] [3]

Procedure	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14 0h	Day 15 24h	Day 16 48h	Day 17 72h	Day 18 96h	Follow-up (7-14 days post last dosing)
QD Dosing with GSK3640254 following moderate fat meal			X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Plasma PK Sampling[5 4]			X	X	X	X		X		X		X		X		X	X	X	X	X	
Plasma Metabolite Sampling[6 5]			X	X												X	X				
Urine ~~PK and~~ Metabolite Sampling[7 6]			X	X												X	X				
PGx Sampling (if participant consents)	~~X~~	**X**																			
Adverse Event Review	<==========																				==========>
Con Med Review	<==========																				==========>
Furlough from Unit																				X	

Note:

1. A Full Physical Exam will include at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. **A single exam can be performed on D-2 or D-1.**
2. **A BMI does not need to be measured at the time of measurement.**
3. ECG data extracted from the Continuous ECG will be assessed before PK sampling, prior to dosing and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4.5, 5, 5.5, 6, 8, 12 h, and 24 h post dose on Day 1 and Day 14 and on corresponding timepoints on Day -1. At timepoints for ECG extraction, subjects will be supinely resting for at least 10 minutes. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should be carried out in said order. The frequency of EKGs will support an exploratory endpoint to evaluate (should clinical development continue) the ER relationship between GSK3640254 and QTcF. Once human data (eg Cmax) is known, the number of EKG time points may be reduced.

4. This pregnancy test will be obtained approximately 37 days after the last dose of study treatment
5. Plasma PK samples for bioanalysis for GSK3640254 will be collected pre-dose ~~(within 15 minutes prior to dosing)~~ **according to the Time Window Allowances as indicated in the Study Reference Manual** and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12 h on Day 1 and Day 14. On dosing days, plasma PK will be collected pre-dose. The number of PK sampling time points may be reduced in the initial MAD cohort as well as further in subsequent MAD dosing groups once human PK data are available in the SAD as well as in the initial MAD cohorts.
6. Plasma Metabolite samples for metabolite identification will be collected pre-dose ~~(within 15 minutes prior to dosing)~~ **according to the Time Window Allowances as indicated in the Study Reference Manual** and at the same time points as for plasma PK samples on Day 1, Day 2 and Day 14, and Day 15. Plasma metabolite samples will not be collected in the expansion cohort.
7. Urine ~~PK and~~ Metabolite Sampling for bioanalysis and metabolite identification will be collected pre-dose ~~(within 1 hour prior to dosing)~~ **according to the Time Window Allowances as indicated in the Study Reference Manual** and from time 0 up to 24 hours on Day 1 and Day 14. Urine samples will not be collected in the expansion cohort.

ADDED TEXT

3.2.2 Preliminary Safety and PK data in Current Study (SAD doses 1, 3, and 10 mg)

Through Amendment 2 of the current protocol, preliminary review of blinded safety data for the 1, 3, and 10 mg doses of the ongoing study indicate no major clinically significant safety or tolerability concerns. There have been 5, 4 and 11 AEs (all non-serious) reported in the 1, 3, and 10 mg doses, respectively (n = 16 randomized subjects). All AEs were single reports, except for three cases of dizziness and three cases of contact dermatitis, related to ECG leads or intravenous cannula site. All AEs were Grade 1, apart from an AE of depression (Grade 2); this AE began eight days after receipt of study medication in Period 1 but was reported 43 days later. On further questioning, depression was associated with difficulty in sleeping and thoughts of self-harm. Immediate evaluation by a psychiatrist and GP uncovered long standing personal and family issues which pre-existed study entry. Given the psychosocial stressors, the depression was unrelated to study drug as determined by the investigator and the Sponsor. The subject was withdrawn from the study in order that treatment with anti-depressant medication could commence. A further subject withdrew from the study due to personal reasons. Only one AE (dizziness in the blinded 10 mg dosing arm) was identified as related to study medication. One subject in the blinded 3 mg arm dosing arm experienced three episodes of intermittent nightmares post dose, all reported as unrelated to study medication. The subject had previously reported nightmares, but in-house, these had occurred more frequently. There have been no on-treatment clinically significant abnormalities in vital signs or ECGs. Finally, review of laboratory findings revealed one subject in the blinded 10 mg dosing arm whose Haematocrit decreased from 45.2% to 41.8% (5 days after dosing).

Preliminary PK parameters for GSK3640254 following single doses of 1, 3, and 10 mg are summarized in Table 1. GSK3640254 is slowly absorbed with maximum concentration observed on average 3.5 hours after dosing and slowly eliminated with an average half-life of 26 hours. In general, exposures were lower along with a longer half-life than predicted based on animal data (Sections 5.5.1 and 5.5.3). The observed Cmax is approximately 75% lower, the AUC is approximately 65% lower and the half-life is about 70% longer. The lower exposures may be due to a lower extent of absorption than the predicted based on the animal data.

Table 1 Summary of Preliminary PK Parameters Following Single Doses of GSK3640254 in study 207187

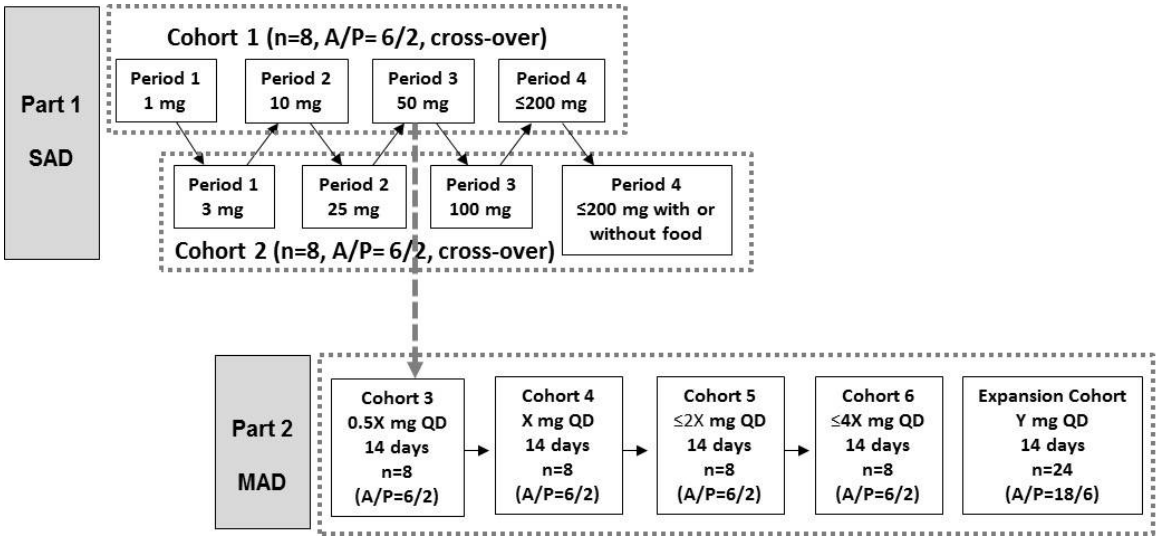
	Dose of GSK3640254		
	1 mg	**3 mg**	**10 mg**
Parameters	N=6	N=6	N=6
Cmax, ng/mL	4.93 (16%)	13.8 (31%)	47.0 (30%)
Tmax, h	3.5 (2.5 – 6.0)	4.5 (2.0 – 5.0)	3.5 (2.5 – 5.0)

T1/2z, h	NR	NR	25.8 (17%)
AUC, ng.h/mL	NR	NR	1230 (19%)
Note: Parameters are summarized as geometric mean (CVb%) except for Tmax presented as median (min-max). NR: not reportable due to limited data in terminal phase and AUC extrapolated being greater than 40%.			

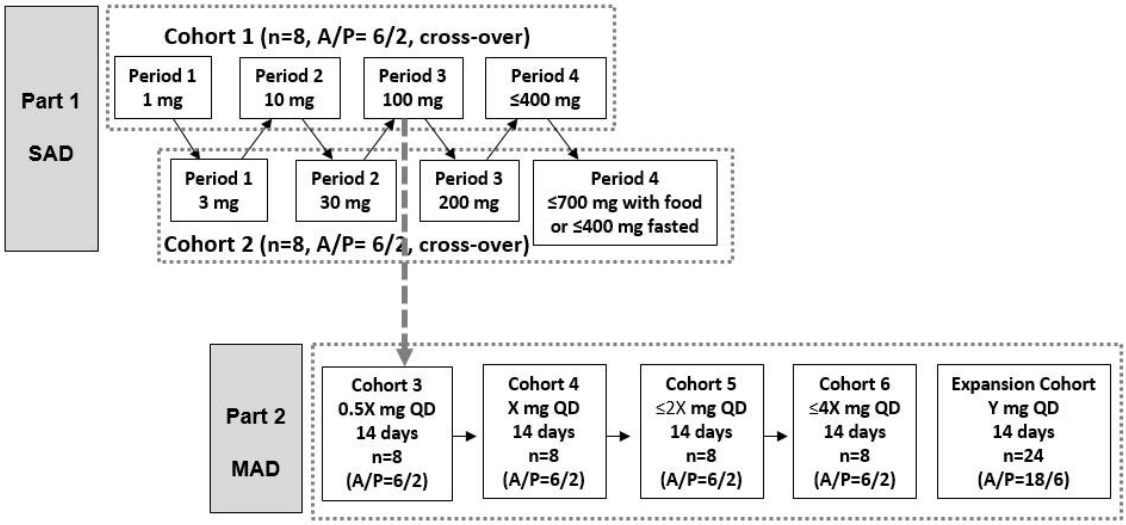
5.1 Overall Design

Figure 2 Phase 1 Study in Healthy Participants using planned doses of GSK3640254

PREVIOUS TEXT



REVISED TEXT



Part 2 (MAD):

PREVIOUS TEXT

The earliest point at which Part 2 (MAD) of the study will be initiated is 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 GSK3640254, noted as X, is anticipated to be that which is predicted to provide a steady state Ctrough ≥ 0.11 μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1 (see Section 5.5.2 for further details). The initial dose in the MAD (Cohort 3) will be approximately half the anticipated minimally effective dose or 0.5X. Dose escalation in the MAD will not exceed 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1).

REVISED TEXT

The earliest point at which Part 2 (MAD) of the study will be initiated is 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 GSK3640254, noted as X, is anticipated to be that which is predicted to provide a steady state Ctrough ≥ 0.11 μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1 (see Section 5.5.2 for further details). The initial dose in the MAD (Cohort 3) will be approximately half the anticipated minimally effective dose or 0.5X. Dose escalation in the MAD will not exceed **approximately** 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1).

5.5.1. Predicted Human Pharmacokinetics

PREVIOUS TEXT

The pharmacokinetic profile for GSK3640254 in humans was predicted using allometric scaling across all species (mouse, rat, dog, and monkey), and was combined with Css-MRT modeling to obtain the predicted human PK profile. Using this method, the IV plasma clearance in humans for GSK3640254 is projected to be low (0.47 mL/min/kg). The intravenous volume of distribution was assumed to be the same as in dogs or close to total body water (0.5 L/kg). The elimination half-life is anticipated to be around 15 hours, leading to a small anticipated accumulation with once daily dosing of ~50%. The mean oral bioavailability in animals was 58% and assumed for exposure projections in humans.

REVISED TEXT

The pharmacokinetic profile for GSK3640254 in humans was predicted using allometric scaling across all species (mouse, rat, dog, and monkey), and was combined with Css-

MRT modeling to obtain the predicted human PK profile. Using this method, the IV plasma clearance in humans for GSK3640254 **was** ~~is~~ projected to be low (0.47 mL/min/kg). The intravenous volume of distribution was assumed to be the same as in dogs or close to total body water (0.5 L/kg). The elimination half-life **was** ~~is~~ anticipated to be around 15 hours, leading to a small anticipated accumulation with once daily dosing of ~50%. The mean oral bioavailability in animals was 58% and assumed for exposure projections in humans.

The emerging PK data obtained at the three lower single doses of 1, 3 and 10 mg are presented in Section 3.2.2.

5.5.2 Predicted Human Effective Dose

PREVIOUS TEXT

The potential minimally effective dose for GSK3640254 was estimated using the predicted human PK profile, assuming similar between-participant PK variability to that observed with GSK3532795 (Population PK model based on data from Phase 2b study AI468038, Metrum Research Group, 2016), to ensure that 95% of participants have steady state trough concentrations that exceed the target concentration of 0.11 μg/mL following once daily dosing of GSK3640254. This led to the prediction of a likely minimally effective once daily dose of approximately 40 mg, assuming 58% bioavailability. At this dose, the mean repeat-dose Cmax is predicted to be approximately 1.11 μg/mL, mean trough concentration is predicted to be approximately 0.290 μg/mL and mean AUC is predicted to be approximately 13.7 μg.h/mL (Table 4). The anticipated steady-state mean AUC is 1.63-fold lower than the NOAEL in the rat, 4.46-fold lower than the LOAEL in the rat, and 5.35-fold lower than the LOAEL in the dog.

The relationship between GSK3640254 exposure and efficacy, duration of antiviral response, and development of on-treatment resistance will be evaluated in future studies in HIV-1-infected participants where assessment of a range of exposures will be important to inform the therapeutic dose range of GSK3640254. One exposure parameter of interest is inhibitory quotient (IQ), where IQ = Ctrough/PBA-EC_{90}. The IQs of other antiretrovirals at approved doses are approximately 19, 27, and 36 for dolutegravir 50 mg once daily, atazanavir 300 mg once daily with ritonavir, and lopinavir 400 mg twice daily with ritonavir, respectively [Van Lunzen, 2012 and Zhu, 2012]. For GSK360254, the minimally effective dose provides a trough concentration of 0.11 ug/mL at steady state in 95% of the participants and represents a geometric mean IQ of 7.92. To facilitate assessment of a range of GSK3640254 IQs in future studies in the target population, doses up to 4 times those of the minimally effective dose are planned for assessment in Part 2 (MAD) in healthy participants. These doses will be administered in accordance with PK and safety stopping criteria (see Section 8.1.3). Projected exposures at the highest anticipated once daily dose in the MAD include a mean repeat-dose Ctrough of 0.87 ug/mL and an IQ of 23.7.

REVISED TEXT

The potential minimally effective dose for GSK3640254 was **initially** estimated using the predicted human PK profile, assuming similar between-participant PK variability to that observed with GSK3532795 (Population PK model based on data from Phase 2b study AI468038, Metrum Research Group, 2016), to ensure that 95% of participants have steady state trough concentrations that exceed the target concentration of 0.11 μg/mL following once daily dosing of GSK3640254. This led to the prediction of a likely minimally effective once daily dose of approximately 40 mg, assuming 58% bioavailability. **After PK information were obtained following administration of 1, 3 and 10 mg of GSK3640254 in this study, a pharmacokinetic model was fit through these data and the observed PK profile was used along with the previously assumed variabilities. The updated minimally effective once daily dose is approximately 70 mg.** At this dose, the mean repeat-dose Cmax is predicted to be approximately ~~1.11~~ **0.544** μg/mL, mean trough concentration is predicted to be approximately ~~0.290~~ **0.238** μg/mL and mean AUC is predicted to be approximately ~~13.7~~ **8.91** μg.h/mL (Table **4**5). The anticipated steady-state mean AUC is ~~1.63~~**2.52**-fold lower than the NOAEL in the rat, ~~4.46~~**6.86**-fold lower than the LOAEL in the rat, and ~~5.35~~ **8.23**-fold lower than the LOAEL in the dog.

The relationship between GSK3640254 exposure and efficacy, duration of antiviral response, and development of on-treatment resistance will be evaluated in future studies in HIV-1-infected participants where assessment of a range of exposures will be important to inform the therapeutic dose range of GSK3640254. One exposure parameter of interest is inhibitory quotient (IQ), where IQ = Ctrough/PBA-EC_{90}. The IQs of other antiretrovirals at approved doses are approximately 19, 27, and 36 for dolutegravir 50 mg once daily, atazanavir 300 mg once daily with ritonavir, and lopinavir 400 mg twice daily with ritonavir, respectively [Van Lunzen, 2012 and Zhu, 2012]. For GSK360254, the minimally effective dose provides a trough concentration of 0.11 ug/mL at steady state in 95% of the participants and represents a geometric mean IQ of 7.92. To facilitate assessment of a range of GSK3640254 IQs in future studies in the target population, doses up to 4 times those of the minimally effective dose are planned for assessment in Part 2 (MAD) in healthy participants. These doses will be administered in accordance with PK and safety stopping criteria (see Section 8.1.3). Projected exposures at the highest anticipated once daily dose in the MAD include a mean repeat-dose Ctrough of ~~0.87~~**1.02** ug/mL and an IQ of ~~23.7~~**27.8**.

5.5.3 Part 1 (SAD) Starting Dose and Dose Escalation

PREVIOUS TEXT

Dose escalations in Part 1 (SAD) will be governed in real-time by safety and PK stopping criteria (see Section 8.1.3 and Section 8.1.4). A dose will not be assessed in the MAD until the anticipated steady-state exposures (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met PK or safety stopping criteria in the SAD portion of the study (Part 1). The maximum dose in the MAD is planned to be approximately 4X, where X is the minimally efficacious dose given once daily (see Section 5.5.2). To account for assumed accumulation of 50% upon repeat dosing, the highest dose in the SAD will be 6X. This will allow single dose evaluation of the highest anticipated steady-state exposures before once daily administration of the highest MAD

dose. Based on the assumptions described above, the anticipated maximum dose in Part 1 is a single dose of 200 mg. The predicted mean single dose Cmax of 200 mg is 3.94 µg/mL. Given different assumptions of with-in and between participant Cmax variability, the probabilities of any participant Cmax being above 7.96 µg/mL, the SAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table 2. All doses in the SAD are governed by safety and PK stopping criteria. A dose which has met formal clinical, QT, or PK stopping criteria will not be repeated in the SAD (or MAD).

Table 2 Probability of any SAD participant (Cmax >7.96 µg/mL) for potential doses

Cmax Variability		Potential GSK3640254 SAD Doses						
%CVw[1]	%CVb[1]	10mg	25mg	50mg	100mg	200mg	250mg	300mg
12.5	25	0	0	0	0	0.034	0.211	0.593
25	25	0	0	0	0	0.122	0.405	0.754
17.5	35	0	0	0	0	0.181	0.486	0.772
35	35	0	0	0	0.013	0.363	0.636	0.831
25	50	0	0	0	0.016	0.436	0.692	0.861
50	50	0	0	0.005	0.101	0.591	0.792	0.905

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

REVISED TEXT

Dose escalations in Part 1 (SAD) will be governed in real-time by safety and PK stopping criteria (see Section 8.1.3 and Section 8.1.4). A dose will not be assessed in the MAD until the anticipated steady-state exposures (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met PK or safety stopping criteria in the SAD portion of the study (Part 1). The maximum dose in the MAD is planned to be approximately 4X, where X is the minimally efficacious dose given once daily (see Section 5.5.2). To account for ~~assumed~~**anticipated** accumulation of ~~50~~**115**% upon repeat dosing, the highest dose in the SAD will be **approximately** ~~6~~**9**X. This will allow single dose evaluation of the highest anticipated steady-state exposures before once daily administration of the highest MAD dose. Based on the assumptions described above, the anticipated maximum dose in Part 1 is a single dose of **up to 700**~~200~~ mg. The predicted mean single dose Cmax of **700**~~200~~ mg is ~~3.94~~**2.74** µg/mL. Given different assumptions of with-in and between participant Cmax variability, the probabilities of any participant Cmax being above 7.96 µg/mL, the SAD PK Stopping Criterion (Section 8.1.3), are

illustrated in Table 2. All doses in the SAD are governed by safety and PK stopping criteria. A dose which has met formal clinical, QT, or PK stopping criteria will not be repeated in the SAD (or MAD).

Table ~~2~~3 Probability of any SAD participant (Cmax >7.96 µg/mL) for potential doses

~~Cmax Variability~~		~~Potential GSK3640254 SAD Doses~~						
~~%CVw[1]~~	~~%CVb[1]~~	~~10mg~~	~~25mg~~	~~50mg~~	~~100mg~~	~~200mg~~	~~250mg~~	~~300mg~~
~~12.5~~	~~25~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0.034~~	~~0.211~~	~~0.593~~
~~25~~	~~25~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0.122~~	~~0.405~~	~~0.754~~
~~17.5~~	~~35~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0.181~~	~~0.486~~	~~0.772~~
~~35~~	~~35~~	~~0~~	~~0~~	~~0~~	~~0.013~~	~~0.363~~	~~0.636~~	~~0.831~~
~~25~~	~~50~~	~~0~~	~~0~~	~~0~~	~~0.016~~	~~0.436~~	~~0.692~~	~~0.861~~
~~50~~	~~50~~	~~0~~	~~0~~	~~0.005~~	~~0.101~~	~~0.591~~	~~0.792~~	~~0.905~~

~~Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation~~

Cmax Variability		Potential GSK3640254 SAD Doses				
%CVw[1]	%CVb[1]	30mg	100mg	200mg	400mg	700mg
7.5	15	0	0	0	0	0
15	15	0	0	0	0	0.001
12.5	25	0	0	0	0	0.005
25	25	0	0	0	0	0.038
17.5	35	0	0	0	0.001	0.071
35	35	0	0	0	0.01	0.191
25	50	0	0	0	0.024	0.261
50	50	0	0	0.007	0.094	0.445

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

5.5.4. Part 2 (MAD) Starting Dose and Dose Escalation

PREVIOUS TEXT

The initial dose in the MAD (Cohort 3) will be approximately half the likely minimally effective dose, re-estimated based on the clinical PK data collected in the early doses of Part 1. Dose escalation in the MAD will not exceed 2-fold between cohorts, and will be governed by both safety and MAD PK stopping criteria (see Section 8.1.3 and Section 8.1.4). Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any participant AUCtau in the MAD above 61.1 μg.hr/mL, the MAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table 3.

Table 3 Probability of any MAD participant (AUCtau > 61.1 μg.h/mL) for potential QD doses

AUC variability	Potential GSK3640254 QD MAD Doses						
%CVb[1]	25mg	50mg	100mg	110mg	120mg	130mg	140mg
0.25	0	0	0.056	0.144	0.269	0.466	0.65
0.35	0	0	0.224	0.378	0.525	0.684	0.81
0.5	0	0.019	0.514	0.653	0.736	0.829	0.876

Note: 1, %CVb: between-participant coefficient of variation

REVISED TEXT

The initial dose in the MAD (Cohort 3) will be approximately half the likely minimally effective dose, re-estimated based on the clinical PK data collected in the early doses of Part 1. Dose escalation in the MAD will not exceed **approximately** 2-fold between cohorts, and will be governed by both safety and MAD PK stopping criteria (see Section 8.1.3 and Section 8.1.4). Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any participant AUCtau in the MAD above 61.1 μg.hr/mL, the MAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table 3.

Table ~~3~~4 Probability of any MAD participant (AUCtau > 61.1 μg.h/mL) for potential QD doses

~~AUC variability~~	~~Potential GSK3640254 QD MAD Doses~~						
~~%CVb[1]~~	~~25mg~~	~~50mg~~	~~100mg~~	~~110mg~~	~~120mg~~	~~130mg~~	~~140mg~~
~~0.25~~	~~0~~	~~0~~	~~0.056~~	~~0.144~~	~~0.269~~	~~0.466~~	~~0.65~~
~~0.35~~	~~0~~	~~0~~	~~0.224~~	~~0.378~~	~~0.525~~	~~0.684~~	~~0.81~~
~~0.5~~	~~0~~	~~0.019~~	~~0.514~~	~~0.653~~	~~0.736~~	~~0.829~~	~~0.876~~

~~Note: 1, %CVb: between-participant coefficient of variation~~

AUC variability	Potential GSK3640254 QD MAD Doses			
%CVb[1]	40mg	80mg	150mg	300mg
0.15	0	0	0	0.009
0.25	0	0	0	0.162
0.35	0	0	0	0.41
0.5	0	0	0.041	0.631

Note: 1, %CVb: between-participant coefficient of variation

5.5.6 Anticipated Exposure and Safety Cover for a Range of Potential Doses

PREVIOUS TEXT

Projected steady-state exposures of GSK3640254 from potential doses in Part 2 are compared to target efficacious concentrations and preclinical toxicity exposures in Table 4. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats and only to a LOAEL in dogs. Findings in both species were GI related, limited and reversible (see Section 3.3.1 and the CIB for details).

Table 4 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

~~Parameter~~	~~10 mg~~	~~20 mg~~	~~40 mg~~	~~80 mg~~	~~120 mg~~
~~Ctrough, ug/mL~~	-	-	-	-	-
~~Mean~~	~~0.0725~~	~~0.145~~	~~0.290~~	~~0.580~~	~~0.870~~
~~Lower bound of 90% CI~~	~~0.0334~~	~~0.0668~~	~~0.134~~	~~0.267~~	~~0.401~~
~~Ctrough/Ctarget~~	-		-		-
~~Mean~~	~~0.659~~	~~1.32~~	~~2.64~~	~~5.27~~	~~7.91~~
~~Lower bound of 90% CI~~	~~0.304~~	~~0.607~~	~~1.215~~	~~2.43~~	~~3.64~~
~~Cmax Day 1, ug/mL~~					
~~Mean~~	~~0.197~~	~~0.394~~	~~0.788~~	~~1.58~~	~~2.36~~
~~Upper bound of 80% CI~~	~~0.348~~	~~0.696~~	~~1.392~~	~~2.78~~	~~4.18~~
~~Cmax Cover with~~	-		-		-
~~Rat NOAEL~~	~~6.81~~	~~3.41~~	~~1.70~~	~~0.851~~	~~0.568~~
~~Dog LOAEL~~	~~12.0~~	~~5.98~~	~~2.99~~	~~1.49~~	~~0.996~~
~~Cmax Day 14, ug/mL~~					
~~Mean~~	~~0.278~~	~~0.556~~	~~1.112~~	~~2.22~~	~~3.34~~
~~Upper bound of 80% CI~~	~~0.420~~	~~0.839~~	~~1.678~~	~~3.36~~	~~5.03~~
~~Cmax Cover with~~	-		-		-
~~Rat NOAEL~~	~~5.65~~	~~2.82~~	~~1.41~~	~~0.706~~	~~0.471~~
~~Dog LOAEL~~	~~9.92~~	~~4.96~~	~~2.48~~	~~1.24~~	~~0.826~~
~~Mean AUC, ug.h/mL~~					
~~Mean~~	~~3.43~~	~~6.86~~	~~13.71~~	~~27.4~~	~~41.1~~
~~Upper bound of 80% CI~~	~~4.84~~	~~9.68~~	~~19.4~~	~~38.7~~	~~58.1~~
~~AUC Cover with~~	-		-		-
~~Rat NOAEL~~	~~4.63~~	~~2.31~~	~~1.16~~	~~0.58~~	~~0.386~~
~~Rat LOAEL~~	~~12.6~~	~~6.31~~	~~3.16~~	~~1.58~~	~~1.05~~
~~Dog LOAEL~~	~~15.1~~	~~7.57~~	~~3.79~~	~~1.89~~	~~1.26~~

Note: The upper bound of the 80% CI is presented to capture the likely highest PK values in 6 subjects. The Cmax and AUC cover were computed as the ratio of Cmax or AUC in animal divided by the Upper Bound of the 80% CI predicted for humans. Ctarget = 3xPBA-EC_{90} (0.11 µg/mL)

REVISED TEXT

Projected steady-state exposures of GSK3640254 from potential doses in Part 2**, taking into consideration the PK emerging from single doses of 1, 3 and 10 mg,** are compared to target efficacious concentrations and preclinical toxicity exposures in Table 4**5**. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats and only to a LOAEL in dogs. Findings in both species were GI related, limited and reversible (see Section 3.3.1 and the CIB for details).

Table 45 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

Parameter	40 mg	80 mg	150 mg	300 mg
Ctrough, ug/mL				
Mean	0.136	0.272	0.509	1.019
Lower bound of 90% CI	0.0680	0.136	0.255	0.510
Ctrough/Ctarget				
Mean	1.23	2.47	4.63	9.26
Lower bound of 90% CI	0.618	1.24	2.32	4.64
Cmax Day 1, ug/mL				
Mean	0.157	0.314	0.588	1.18
Upper bound of 80% CI	0.360	0.720	1.35	2.70
Cmax Cover with				
Rat NOAEL	6.59	3.293	1.756	0.878
Dog LOAEL	11.56	5.780	3.083	1.541
Cmax Day 14, ug/mL				
Mean	0.311	0.622	1.17	2.33
Upper bound of 80% CI	0.484	0.968	1.82	3.63
Cmax Cover with				
Rat NOAEL	4.90	2.448	1.306	0.653
Dog LOAEL	8.60	4.298	2.292	1.146
Mean AUC, ug.h/mL				
Mean	5.09	10.2	19.1	38.17
Upper bound of 80% CI	7.26	14.5	27.2	54.49
AUC Cover with				
Rat NOAEL	3.08	1.542	0.822	0.411
Rat LOAEL	8.41	4.205	2.243	1.12
Dog LOAEL	10.09	5.04	2.69	1.35

Note: The upper bound of the 80% CI is presented to capture the likely highest PK values in 6 subjects. The Cmax and AUC cover were computed as the ratio of Cmax or AUC in animal divided by the Upper Bound of the 80% CI predicted for humans. Ctarget = 3xPBA-EC_{90} (0.11 µg/mL). These predictions are taking into consideration the emerging PK observed after single administration of 1, 3 and 10 mg.

6.4 Screen Failures

PREVIOUS TEXT

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria that established screen failure, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

REVISED TEXT

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. **However, reserve participants only need to undergo the screening process once every 90 days; additionally, reserve participants will still be subject to Day -2 and -1 evaluations in routine fashion (as shown in the SoA table).** A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria that established screen failure, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

9 STUDY ASSESSMENTS AND PROCEDURES

ADDED TEXT

- Time window allowances for all study assessments will be followed according to the time window allowances as indicated in the SRM.

9.5 Pharmacokinetics

PREVIOUS TEXT

- Urine samples will be collected for 24 hours on Day 1 and Day 14 in MAD cohorts 3, 4, 5 and 6 for measurement of urine concentrations of GSK3640254 as specified in the **SoA**. After PK analysis, aliquots of 200 mL pooled urine samples (0-24 hour) will be used for metabolite profiling. A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual start and stop date and time (24-hour clock time) as well as collected volume over 24 hours will be recorded for urine sample. Details of PK urine sample collection, processing, storage procedures and shipping procedures are detailed in the SRM.

REVISED TEXT

- Urine samples will be collected for 24 hours on Day 1 and Day 14 in MAD cohorts 3, 4, 5 and 6 for measurement of urine concentrations of GSK3640254 as specified in the **SoA**. ~~After PK analysis, aliquots of 200 mL pooled urine samples (0-24 hour) will be used for metabolite profiling. A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual start and stop date and time (24-hour clock time) as well as collected volume over 24~~

~~hours will be recorded for urine sample. Details of PK urine sample collection, processing, storage procedures and shipping procedures are detailed in the SRM.~~

10.3.3. Interim Analyses

PREVIOUS TEXT

In this part, we want to explore the operating characteristics of the 200mg dose. Given different assumptions of with-in and between participant Cmax variability (CV%), and assuming dose proportionality (slope=1), data for 1000 trials were simulated based on Whitehead's model [1]. Each simulated trial contains Cmax values for 6 subjects on treatment for doses ranging from 1mg to 100mg in SAD cohort 1 and cohort 2.

For each simulate trial, we fitted the mixed effect Bayesian model based on mode [1]. In the following procedure, we calculated the Bayesian probability of an individual exceeding the Cmax threshold:

We had 10000 iterations in the MCMC procedure. In each iteration, we obtained the estimated parameters $\hat{\theta}_1, \hat{\theta}_2, \hat{s}_i (i = 1,2, \dots ,6)$ and $\hat{\sigma}^2$(the estimated standard deviation of ϵ_{ij}), Based on the estimation, a random sample for each subject, which represented the simulated exposure in the 200mg dose, was drawn from the distribution $N(\hat{\theta}_1 + \hat{\theta}_2 \cdot 200 + \hat{s}_i, \hat{\sigma}^2)$. We counted the number of iterations N with any simulated exposure exceeding the Cmax threshold log(7.96). The Bayesian probability was calculated as $1 - \frac{N}{10000}$.

For each trial, the Bayesian probability for the 200mg dose is calculated and compared with different thresholds (40%, 50% or 60%). Among those 1000 trials, the percentages of trials with Bayesian probability below the thresholds, which stands for the percentage of trials that could be escalated to dose 200mg, are listed in Table 7.

Table 7 Percentage of trials with Bayesian probability less than the threshold (40%, 50% or 60%)

Cmax Variability		**Probability Threshold**		
%CVw[1]	**%CVb[1]**	**40%**	**50%**	**60%**
12.5	25	98.3%	98.8%	99.1%
25	25	93.9%	96.5%	98.4%
17.5	35	83.5%	87.3%	90.8%
35	35	69.4%	79.0%	86.3%
25	50	55.3%	63.0%	70.1%
50	50	33.8%	47.9%	58.9%

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

Based on the table above, when with-in and between participant Cmax variability are small or moderate, the probability of successfully escalating to 200mg is high.

REVISED TEXT

In this part, we want to explore the operating characteristics of the ~~200~~**700**mg dose **for SAD**. Given different assumptions of with-in and between participant Cmax variability (CV%), and assuming dose proportionality (slope=1), data for 1000 trials were simulated based on Whitehead's model [1]. Each simulated trial contains Cmax values for 6 subjects on treatment for doses ranging from 1mg to ~~100~~**400**mg in SAD cohort 1 and cohort 2.

For each simulate trial, we fitted the mixed effect Bayesian model based on mode [1]. In the following procedure, we calculated the Bayesian probability of an individual exceeding the Cmax threshold:

We had 10000 iterations in the MCMC procedure. In each iteration, we obtained the estimated parameters $\hat{\theta}_1, \hat{\theta}_2, \hat{s}_i (i = 1,2, \ldots, 6)$ and $\hat{\sigma}^2$(the estimated standard deviation of ϵ_{ij}), Based on the estimation, a random sample for each subject, which represented the simulated exposure in the ~~200~~**700**mg dose, was drawn from the distribution $N(\hat{\theta}_1 + \hat{\theta}_2 \cdot 200 + \hat{s}_i, \hat{\sigma}^2)$. We counted the number of iterations N with any simulated exposure exceeding the Cmax threshold log(7.96). The Bayesian probability was calculated as $1 - \frac{N}{10000}$.

For each trial, the Bayesian probability for the ~~200~~**700**mg dose is calculated and compared with different thresholds (40%, 50% or 60%). Among those 1000 trials, the percentages of trials with Bayesian probability below the thresholds, which stands for the percentage of trials that could be escalated to dose ~~200~~**700**mg, are listed in Table 7.

Table ~~7~~8 Percentage of trials with Bayesian probability less than the threshold (40%, 50% or 60%)

~~Cmax Variability~~		~~Probability Threshold~~		
~~%CVw[1]~~	~~%CVb[1]~~	~~40%~~	~~50%~~	~~60%~~
~~12.5~~	~~25~~	~~98.3%~~	~~98.8%~~	~~99.1%~~
~~25~~	~~25~~	~~93.9%~~	~~96.5%~~	~~98.4%~~
~~17.5~~	~~35~~	~~83.5%~~	~~87.3%~~	~~90.8%~~
~~35~~	~~35~~	~~69.4%~~	~~79.0%~~	~~86.3%~~
~~25~~	~~50~~	~~55.3%~~	~~63.0%~~	~~70.1%~~
~~50~~	~~50~~	~~33.8%~~	~~47.9%~~	~~58.9%~~

~~Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation~~

Cmax Variability		**Probability Threshold**		
%CVw[1]	**%CVb[1]**	**40%**	**50%**	**60%**
7.5	15	100.0%	100.0%	100.0%
15	15	100.0%	100.0%	100.0%
12.5	25	99.9%	100.0%	100.0%
25	25	99.3%	99.5%	99.8%
17.5	35	95.6%	97.0%	98.5%
35	35	91.0%	94.0%	97.1%
25	50	75.7%	81.9%	85.2%
50	50	53.9%	66.8%	77.0%

Note: 1, %CVw: within-participant coefficient of variation. %CVb: between-participant coefficient of variation

Based on the table above, when with-in and between participant Cmax variability are small or moderate, the probability of successfully escalating to ~~200~~**700**mg is high.

Amendment: 04; 17-May-2018

ADDED TEXT

Overall Rationale for the Protocol Amendment:

The purpose of this protocol amendment (04) is to study a higher dose of 320 mg QD for 14 days in the MAD part of the study (see Cohort 6 in Figure 1). The MAD 320 mg QD dose would explore steady-state Cmax values greater than those explored in the SAD study (which is not permitted by the current version of the protocol). This dose of 320 mg QD is four times the projected minimum effective dose (~80 mg QD) and is in line with the MAD PK stopping Criteria in the current approved protocol (amendment 03/ 05 December 2017); specifically, the probability of any subject having an AUC > 61.1 µg/mL is 42% (data through May 9, 2018). A MAD dose of 320 mg QD allows for a thorough evaluation of PK/QT relationship and a greater safety margin in subsequent clinical trials in patients.

The totality of preliminary PK and safety/tolerability data to date shows the MAD 320 mg QD dose is clinically and scientifically reasonable (see Section 3.2.2 for full details). Specifically, GSK3640254 following single dose administration ultimately showed a plateauing of exposure at the 700 mg dose. On Day 14, the mean Cmax for the MAD 200 mg dose (1841 ng/ml in Cohort 5) approximated that seen in the SAD at 400 and 700 mg doses (1881 and 1761 ng/ml, respectively). Since the current protocol does not permit a dose in the MAD to surpass the Cmax studied in the SAD, the ViiV/ GSK Dose Escalation Committee opened the Expansion Cohort (currently ongoing) with a 200 mg dose (See Figure 1) at the conclusion of Cohort 5. Briefly, there have been no significant clinical safety/tolerability findings in the SAD or MAD through May 7, 2018. Preliminary ongoing data review show no deaths or SAEs. There have been 4 individual AEs leading to discontinuation. There have been 10 individual AEs related to blinded study medication. Preliminary review of blinded safety data for the: 1) SAD show 17 subjects experienced 60 individual AEs (58 Grade 1; Two Grade 2) and 2) MAD show 23 subjects experienced 79 individual AEs (77 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System and Gastrointestinal Disorders without a dose/AE relationship. Subjects recruited for the 320 mg QD Cohort will have the same inclusion/exclusion criteria, have the same study and subject stopping criteria, and undergo the same intensive safety evaluation as previously treated subjects in the MAD. Combined, based upon the preliminary safety and PK data gathered to date (see Section 3.2.2 for full details) subjects will be adequately monitored.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Figure 1 changed and MAD Expansion Cohort Dose added	.The actual doses for all Cohorts and Periods updated for the SAD and MAD
Section 3.2.2	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 3.3 Benefit Risk Assessment	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting an unchanged benefit risk assessment for a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 5.1 Overall Design	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)
Section 5.5.2 Predicted Human Effective Dose	Preliminary Safety and PK data from SAD and MAD updated/added	The clinical and PK data is needed to justify the rationale for supporting a proposed dose of 320 mg QD in the MAD (Cohort 6)

List of Specific Changes

Overall Design:

PREVIOUS TEXT

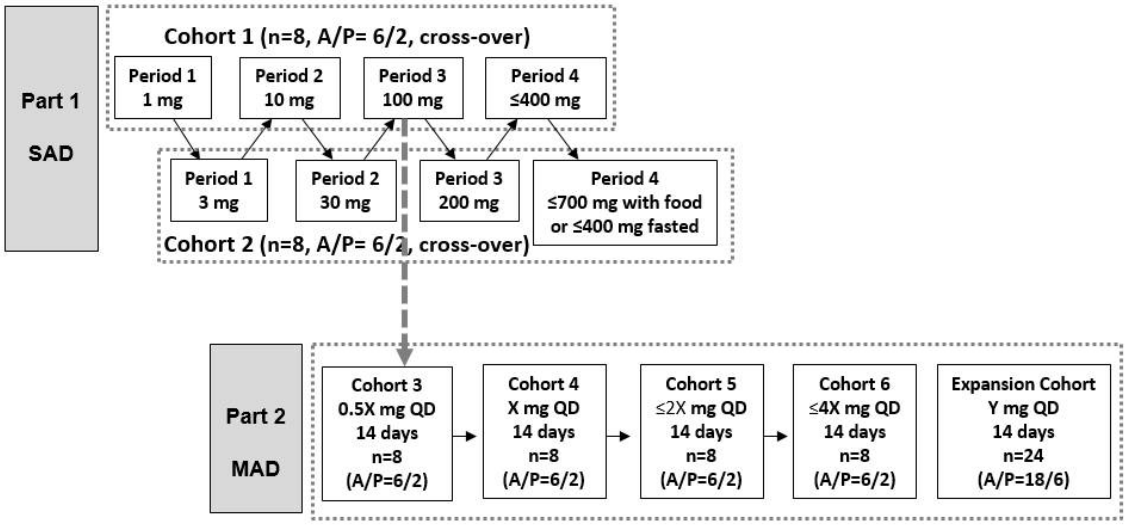
A summary of the overall study design, including proposed doses, sample size, and order, is presented in Figure 1; Schedule of Activities (**SoA**) tables are included in Section 2.

REVISED TEXT

A summary of the overall study design, including ~~proposed~~ doses, sample size, and order, is presented in Figure 1; Schedule of Activities (**SoA**) tables are included in Section 2.

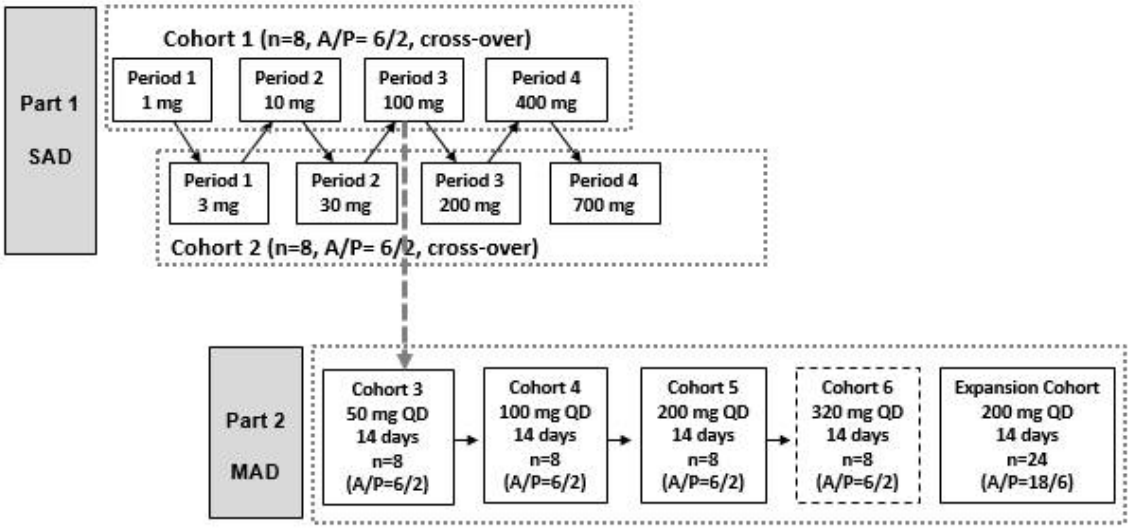
Figure 3 Phase 1 Study in Healthy Participants using planned doses of GSK3640254

PREVIOUS TEXT



Note: A=active, P=placebo. The doses shown here are intended to demonstrate general concepts relating to factors of escalation. X represents the predicted minimally efficacious dose. Y (in the expansion cohort alone) represents a dose previously studied in the multiple ascending dose (MAD) cohorts that did not meet the safety or PK stopping criteria. In Cohort 2 Period 4, a previous dose that was tolerated under fed conditions may be given under fasted conditions to assess food effect.

REVISED TEXT



Note: A=active, P=placebo. The doses shown here ~~are~~ **were/are being completed**. ~~intended to demonstrate general concepts relating to factors of escalation. X represents the predicted minimally efficacious dose. Y (in the expansion cohort alone) represents a dose previously studied in the multiple ascending dose (MAD) cohorts that did not meet the safety or PK stopping criteria. In Cohort 2 Period 4, a previous dose that was tolerated under fed conditions may be given under fasted conditions to assess food effect~~. **Amendment 04 proposes to evaluate a 320 mg Daily dose in MAD Cohort 6.**

Treatment Groups and Duration:

Part 2 (MAD):

PREVIOUS TEXT

Part 2 also includes an Expansion Cohort to evaluate the rate of gastrointestinal (GI) intolerability in 24 participants (active/PBO =18/6). The expansion cohort will be conducted once the evaluation of the safety and PK from Cohorts 3 – 6 are available. The dose Y mg (see Figure 1, MAD) will be one of the previously studied doses that met neither safety nor PK stopping criteria.

REVISED TEXT

Part 2 also includes an Expansion Cohort to evaluate the rate of gastrointestinal (GI) intolerability in 24 participants (active/PBO =18/6). The expansion cohort ~~will be~~ **was** conducted once the evaluation of the safety and PK from Cohorts 3 – ~~6 are~~ **5 were** available. The dose ~~Y~~ **chosen was 200** mg (see Figure 1, MAD). ~~will be one of the previously studied doses that met neither safety nor PK stopping criteria.~~

PREVIOUS TEXT

3.2.2 Preliminary Safety and PK data in Current Study (SAD doses 1, 3, and 10 mg)

Through Amendment 2 of the current protocol, preliminary review of blinded safety data for the 1, 3, and 10 mg doses of the ongoing study indicate no major clinically significant safety or tolerability concerns. There have been 5, 4 and 11 AEs (all non-serious) reported in the 1, 3, and 10 mg doses, respectively (n = 16 randomized subjects). All AEs were single reports, except for three cases of dizziness and three cases of contact dermatitis, related to ECG leads or intravenous cannula site. All AEs were Grade 1, apart from an AE of depression (Grade 2); this AE began eight days after receipt of study medication in Period 1 but was reported 43 days later. On further questioning, depression was associated with difficulty in sleeping and thoughts of self-harm. Immediate evaluation by a psychiatrist and GP uncovered long standing personal and family issues which pre-existed study entry. Given the psychosocial stressors, the depression was unrelated to study drug as determined by the investigator and the Sponsor. The subject was withdrawn from the study in order that treatment with anti-depressant medication could commence. A further subject withdrew from the study due to personal reasons. Only one AE (dizziness in the blinded 10 mg dosing arm) was identified as related to study medication. One subject in the blinded 3 mg arm dosing arm experienced three episodes of intermittent nightmares post dose, all reported as unrelated to study medication. The subject had previously reported nightmares, but in-house, these had occurred more frequently. There have been no on-treatment clinically significant abnormalities in vital signs or ECGs. Finally, review of laboratory findings revealed one subject in the blinded 10 mg dosing arm whose Haematocrit decreased from 45.2% to 41.8% (5 days after dosing).

Preliminary PK parameters for GSK3640254 following single doses of 1, 3, and 10 mg are summarized in Table 1. GSK3640254 is slowly absorbed with maximum concentration observed on average 3.5 hours after dosing and slowly eliminated with an average half-life of 26 hours. In general, exposures were lower along with a longer halflife than predicted based on animal data (Section 5.5.1 and Section 5.5.3). The observed Cmax is approximately 75% lower, the AUC is approximately 65% lower and the halflife is about 70% longer. The lower exposures may be due to a lower extent of absorption than predicted based on the animal data.

Table 1 Summary of Preliminary PK Parameters Following Single Doses of GSK3640254 in study 207187

	Dose of GSK3640254		
	1 mg	**3 mg**	**10 mg**
Parameters	N=6	N=6	N=6
Cmax, ng/mL	4.93 (16%)	13.8 (31%)	47.0 (30%)
Tmax, h	3.5 (2.5 – 6.0)	4.5 (2.0 – 5.0)	3.5 (2.5 – 5.0)
T1/2z, h	NR	NR	25.8 (17%)
AUC, ng.h/mL	NR	NR	1230 (19%)
Note: Parameters are summarized as geometric mean (CVb%) except for Tmax presented as median (min-max). NR: not reportable due to limited data in terminal phase and AUC extrapolated being greater than 40%.			

REVISED TEXT

3.2.2 Preliminary Safety and PK data in Current Study (SAD doses 1, ~~3, and~~ - 7010 mg and MAD doses 50 – 200 mg daily)

~~Through Amendment 2 of the current protocol, preliminary review of blinded safety data for the 1, 3, and 10 mg doses of the ongoing study indicate no major clinically significant safety or tolerability concerns. There have been 5, 4 and 11 AEs (all non-serious) reported in the 1, 3, and 10 mg doses, respectively (n = 16 randomized subjects). All AEs were single reports, except for three cases of dizziness and three cases of contact dermatitis, related to ECG leads or intravenous cannula site. All AEs were Grade 1, apart from an AE of depression (Grade 2); this AE began eight days after receipt of study medication in Period 1 but was reported 43 days later. On further questioning, depression was associated with difficulty in sleeping and thoughts of self-harm. Immediate evaluation by a psychiatrist and GP uncovered long standing personal and family issues which pre-existed study entry. Given the psychosocial stressors, the depression was unrelated to study drug as determined by the investigator and the Sponsor. The subject~~

~~was withdrawn from the study in order that treatment with anti-depressant medication could commence. A further subject withdrew from the study due to personal reasons. Only one AE (dizziness in the blinded 10 mg dosing arm) was identified as related to study medication. One subject in the blinded 3 mg arm dosing arm experienced three episodes of intermittent nightmares post dose, all reported as unrelated to study medication. The subject had previously reported nightmares, but in-house, these had occurred more frequently. There have been no on-treatment clinically significant abnormalities in vital signs or ECGs. Finally, review of laboratory findings revealed one subject in the blinded 10 mg dosing arm whose Haematocrit decreased from 45.2% to 41.8% (5 days after dosing).~~

~~Preliminary PK parameters for GSK3640254 following single doses of 1, 3, and 10 mg are summarized in Table 1. GSK3640254 is slowly absorbed with maximum concentration observed on average 3.5 hours after dosing and slowly eliminated with an average half-life of 26 hours. In general, exposures were lower along with a longer halflife than predicted based on animal data (Section 5.5.1 and Section 5.5.3). The observed Cmax is approximately 75% lower, the AUC is approximately 65% lower and the halflife is about 70% longer. The lower exposures may be due to a lower extent of absorption than predicted based on the animal data.~~

Overall, there have been no major clinical safety/tolerability findings in the SAD (single doses up to 700 mg) or MAD (14 days of dosing up to 200 mg) through May 7, 2018. There have been 20 subjects treated in the blinded SAD and 33 subjects treated in the blinded MAD. Preliminary ongoing data review show no deaths or SAEs. There have been 4 individual AEs leading to discontinuation from the trial:

- **Blinded SAD 10 mg arm: Depression (Grade 2, not related).**
- **Blinded SAD 10 mg arm: Viral Infection (Grade 1, not related) lasting two days**
- **Blinded SAD 100 mg arm: Viral Infection (Grade 1, not related) lasting seven days**
- **Blinded MAD 200 mg arm: Rash Maculopapular (Grade 1, related). This rash occurred 8 days after receiving study medication and lasted for 6 days. There were no laboratory abnormalities. A Dermatology Consultant concluded this was a drug rash and the subject later received fexofenadine 180 mg once daily with a topical steroid cream.**

There have been 10 individual AEs related to study medication (9 Grade 1; One Grade 2):

- **Blinded SAD 10 mg arm: Dizziness**
- **Blinded SAD 30 mg arm: Diarrhea and Abdominal Pain**
- **Blinded SAD 700 mg arm: Diarrhea**
- **Blinded MAD 50 mg arm: Headache (the only G2 related AE), Fatigue, and Transaminases Elevated. The subject with elevated transaminases had peak ALT of 83 IU/L on Day 16 after study medication. The remaining LFTs were normal throughout. An Ultrasound showed a subcapsular area of**

heterogenous echogenicity within segment 7, measuring approximately 35 x 23 x 36 mm. A follow up MRI was normal.

- **Blinded MAD 200 mg arm: Lethargy, Nausea, and Rash Maculopapular.**

Preliminary review of blinded safety data (see Table 1) for the SAD 1 - 700 mg doses show 17 subjects experienced 60 individual AEs (58 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System (16 individual AEs) and Gastrointestinal Disorders (11 individual AEs). The most frequent AEs have been Headache (10 individual AEs), Diarrhea and Contact Dermatitis (5 individual AEs each), and Dizziness (4 individual AEs). There were four Psychiatric individual AEs (three of which have occurred at 1 and 3 mg single blinded arms): Depression, Insomnia, and Nightmare (two individual AEs). There were no Cardiac AEs. There has been no dose/AE relationship.

Preliminary review of blinded safety data (see Table 2) for the MAD 50 – 200 mg (Daily for Fourteen Days) show 23 subjects experienced 79 individual AEs (77 Grade 1; Two Grade 2). The two most frequent AE SOCs have been Nervous System (25 AEs) and Gastrointestinal Disorders (12 individual AEs). The most frequent AEs have been Headache (11 individual AEs), Dizziness (6 individual AEs), and Fatigue (5 individual AEs). There has been no clinically relevant GI or neurologic AE/dose relationship. One subject in the blinded 200 mg arm accounted for 13 individual AEs (5 of which were in the Neurologic SOC). There were three Psychiatric individual AEs: Agitation, Abnormal Dreams, and Nightmare. There was one Cardiac AE (palpitations in the 200 mg blinded dose).

There were no clinically significant abnormal fluctuations or trends in vital signs in the SAD or MAD. There were no abnormal clinically significant arrhythmias or QTcF prolongations observed for any subject in the SAD or MAD. There were no laboratory abnormality trends across doses that were clinically significant or associated with any symptoms.

Table 1: Summary Table (all AEs) in blinded SAD 1 - 700 mg doses

		AEs by Blinded SAD Cohort/Period							
SOC	PT	1 mg	3 mg	10 mg	30 mg	100 mg	200 mg	400 mg	700 mg
Nervous System Disorders	Dizziness	1	1	1					1
	Headache	1		1	2	2	2	2	
	Parasthesia			1					
	Migraine			1					
Gastrointestinal Disorders	Vomitting					2			
	Feces Soft	1							
	Diarrhea			1	1	2			1
	Abdominal Pain				1				
	Feces Discolored					1			

	Feces Pale							1	
Infections and Infestations	Nasopharyngitis			1		1		1	
	Oral Herpes				1				
	Viral Infection			1		1			
	Upper Respiratory Tract Infection						1		
Respiratory, Thoracic, and Mediastinal Disorders	Nasal Obstruction			2					1
	Cough			1		1			
	Oropharyngeal Pain							1	
	Hemoptysis							1	
Skin and Subcutaneous Disorders	Contact Dermatitis	1	1	1			1	1	
Psychiatric Disorders	Depression	1							
	Insomnia	1							
	Nightmare		1						1
Injury, Poisoning, and Procedural Complications	Face Injury	1							
	Skin Abrasion						1		
	Contusion			1					
	Limb Injury	1							
General Disorders and Administration Site Conditions	Catheter site pain			1					
	Vessel Puncture Site Bruise		1						
	Chest Pain	1							
Investigations	Transaminases Increased						1		1
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal Pain				1				
Total AEs by Blinded SAD Cohort/Period		9	4	13	6	10	6	7	5

Table 2: Summary Table (all AEs) in blinded MAD 50 – 200 mg doses

		AEs by Blinded MAD Cohort/Period

SOC	PT	50 mg	100 mg	200 mg
Nervous System Disorders	Dizziness	1	2	3
	Headache	4	2	5
	Somnolence	1		
	Disturbance in Attention			2
	Lethargy			2
	Dizziness Postural			1
	Hypoaesthesia			1
	Dysgeusia			1
Gastrointestinal Disorders	Lip Dry	1		
	Mouth Ulceration	1		
	Aphthous Ulcer	1		
	Abdominal Pain	1		1
	Abdominal Distention		1	1
	Glossodynia			1
	Constipation			2
	Nausea			1
	Gastroesophageal Reflux Disease			1
General Disorders and Administration Site Conditions	Catheter site pain			1
	Vessel Puncture Site Bruise		1	1
	Fatigue	2	2	1
	Feeling Cold	1		
	Catheter site Bruise			1
Skin and Subcutaneous Disorders	Contact Dermatitis	1		2
	Blister		1	
	Dry Skin		1	
	Rash			1
	Rash Maculopapular			1
	Pruitis			1
Musculoskeletal and Connective Tissue Disorders	Back pain	1	1	2
	Musculoskeletal Stiffness	1		
	Muscle Twitching		1	
Injury, Poisoning, and Procedural Complications	Laceration			1
	Contusion	1	1	2

Infections and Infestations	Hordeolum		1	
	Abscess		1	
	Oral Herpes			1
Psychiatric Disorders	Agitation		1	
	Abnormal Dreams			1
	Nightmare		1	
Ear and Labyrinth Disorders	Ear Discomfort			1
	Excessive Cerumen Production			1
Renal and Urinary Disorders	Pollakiuria			1
	Dysuria			1
Respiratory, Thoracic, and Mediastinal Disorders	Epistaxis	1		
Investigations	Transaminases Increased	1		
Cardiac Disorders	Palpitations			1
Total AEs by Blinded MAD Cohort/Period		19	17	43

Preliminary PK parameters for GSK3640254 following single dose administration from 1 to 700 mg are summarized in Table 3. GSK3640254 is slowly absorbed with maximum concentration observed on average 3-4 hours after dosing and slowly eliminated with an average half-life of 24 hours. Cmax and AUC increased in a close to dose proportional manner from 1 to 400 mg with a plateauing in exposure at the 700 mg dose. The maximum observed mean Cmax for the single dose administration (Table 3) is 1881 ng/mL at the dose of 400 mg. The maximum observed mean AUC(0-inf) for the single dose administration (Table 3) is 43116 ng.hr/mL at the dose of 400 mg. The mean exposure observed at 700 mg is slightly lower than that at 400 mg single administration and thus we anticipate similar exposures with doses greater than 700 mg.

Table ~~13~~ 13 Summary of Preliminary PK Parameters Following Single Doses of GSK3640254 in study 207187

	~~**Dose of GSK3640254**~~		
	~~**1 mg**~~	~~**3 mg**~~	~~**10 mg**~~

~~**Parameters**~~	~~N=6~~	~~N=6~~	~~N=6~~
~~Cmax, ng/mL~~	~~4.93 (16%)~~	~~13.8 (31%)~~	~~47.0 (30%)~~
~~Tmax, h~~	~~3.5 (2.5 - 6.0)~~	~~4.5 (2.0 - 5.0)~~	~~3.5 (2.5 - 5.0)~~
~~T1/2z, h~~	~~NR~~	~~NR~~	~~25.8 (17%)~~
~~AUC, ng.h/mL~~	~~NR~~	~~NR~~	~~1230 (19%)~~

~~Note: Parameters are summarized as geometric mean (CVb%) except for Tmax presented as median (min-max).~~

~~NR: not reportable due to limited data in terminal phase and AUC extrapolated being greater than 40%.~~

	Dose							
	1 mg	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**200 mg**	**400 mg**	**700 mg**
PK Parameter	**Geometric Mean (CV%) [N]***							
Cmax	4.9 (16) [6]	13.8 (31) [6]	47 (30) [6]	129.8 (21) [6]	372.1 (72) [6]	578.9 (27) [6]	1881 (50) [6]	1760.8 (44) [6]
Tmax	3.5 (2.5-6) [6]	4.5 (2-5) [6]	3.5 (2.5-5) [6]	4 (2.5-5) [6]	3.8 (2-5) [6]	3 (2-4) [6]	3.3 (2-6) [6]	3.3 (2-4.5) [6]
T1/2(z)	NC	22 (14) [6]	25.8 (17) [6]	23.3 (16) [6]	23.9 (14) [6]	23.2 (17) [6]	23.3 (16) [6]	22.2 (28) [6]
AUC	NC	340 (29) [6]	1229.3 (19) [6]	3008 (26) [6]	8566.4 (67) [6]	14978 (41) [6]	43115.7 (52) [6]	39972.5 (50) [6]
* Tmax has been reported as Median (Min - Max)								
AUC represents AUC(0-inf); NC: Not Computed								
Units: Cmax in ng/mL, AUC in ng.h/mL, t1/2 and tmax in hours								

Preliminary PK parameters on Day 1 and Day 14 for GSK3640254 following repeat dose administration of 50, 100 and 200 mg for 14 days are summarized in Table 4. The exposures on Day 14 are on average 2-3 folds higher than that on Day 1. Cmax and AUC on Day 14 tended to increase in a close to dose proportional manner from 50 to 200 mg. The maximum observed mean Cmax for the repeat dose administration is 1528 ng/mL at the dose of 200 mg on Day 14. The maximum observed mean AUC(0-24) for the repeat dose administration is 23046 ng.hr/mL at the dose of 200 mg on Day 14.

The anticipated mean Cmax at a proposed dose of 320 mg based on the observed exposures (Table 4) using a dose proportionality model is predicted to be 1030 ng/mL on Day 1 and 2475 ng/mL for Day 14. The anticipated mean AUC(0-24) on Day 14 at a proposed dose of 320 mg based on observed exposures (Table 4) using a

dose proportionality model is predicted to be 37942 ng.hr/mL. The probability of any subject exceeding the PK stopping criteria for MAD study with the dose of 320 mg repeat dosing, which is AUC(0-24) of 61100 ng.hr/mL based on LOAEL exposure in rat at 30 mg/kg, is 42% based on data collected through 9th May. The probability of any subject exceeding the PK stopping criteria for SAD study with the dose of 320 mg repeat dosing, which is a Cmax of 7960 ng/mL based on minimal QT effects observed in one dog, is 0.7% based on data collected through 9th May 2018.

Table 4 Summary of Preliminary PK Parameters Following Repeat Dose administration of GSK3640254 in study 207187

	Day 1			Day 14		
	Dose			Dose		
	50 mg	100 mg	200 mg	50 mg	100 mg	200 mg
PK Parameter	Geometric Mean (CV%) [N]*					
AUC l(0-24)	2867.4 (30) [6]	6826.2 (23) [6]	8947.1 (49) [NP]	6285.6 (34) [6]	17537.5 (14) [6]	23046.2 (36) [NP]
Cmax	214.5 (24) [6]	535.6 (23) [6]	689.2 (40) [NP]	413.5 (32) [6]	1182 (10) [6]	1528.4 (30) [NP]
T1/2(z)	NC	NC	NC	24.5 (8) [6]	28.6 (19) [6]	21.9 (12) [NP]
Tmax	3.8 (3-5) [6]	4.3 (2-5) [6]	4 (1.5-5.5) [NP]	3.8 (2.5-5) [6]	4 (1.5-4.5) [6]	3.5 (2-5) [NP]
* Tmax has been reported as Median (Min - Max)						
Units: Cmax in ng/mL, AUC in ng.h/mL and Tmax in hours						
NP: Not Printed as the expansion cohort is still running. This includes 6 active subjects from Cohort 5 and the subjects from expansion cohort 7 studied thruMay 9th, 2018.						
NC: Not Computed						

3.3 Benefit/Risk Assessment

ADDED TEXT

The clinical data gathered through May 7, 2018 is summarized in Section 3.2.2. Overall, there have been no major clinical safety/tolerability findings in the SAD (single doses up to 700 mg) or MAD (14 days of dosing up to 200 mg). The proposed amendment seeks to evaluate a higher dose (320 mg Daily) in the MAD. The probability of the AUC(tau) exceeding the established PK stopping criteria is 42%. Subjects recruited for the 320 mg QD dose in Cohort 6 will have the same inclusion/exclusion criteria, have the same study and subject stopping criteria, and undergo the same safety evaluation. Based upon the preliminary safety and PK data gathered to date (see Section 3.2.2) subjects will be adequately monitored.

3.3.3 Overall Benefit:Risk Conclusion

PREVIOUS TEXT

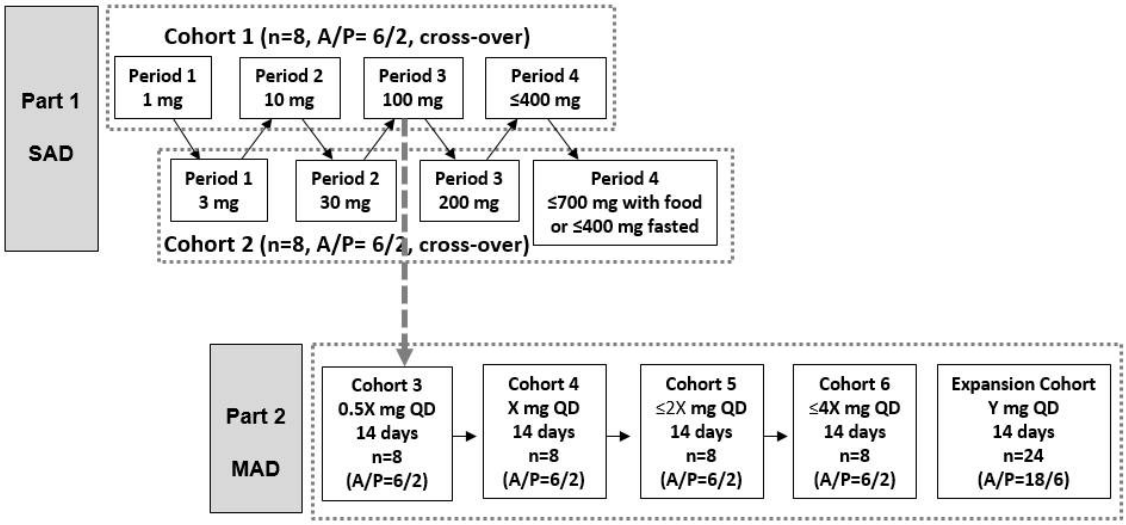
Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable.

ADDED TEXT

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), **the preliminary clinical data gathered through May 7, 2018** and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable.

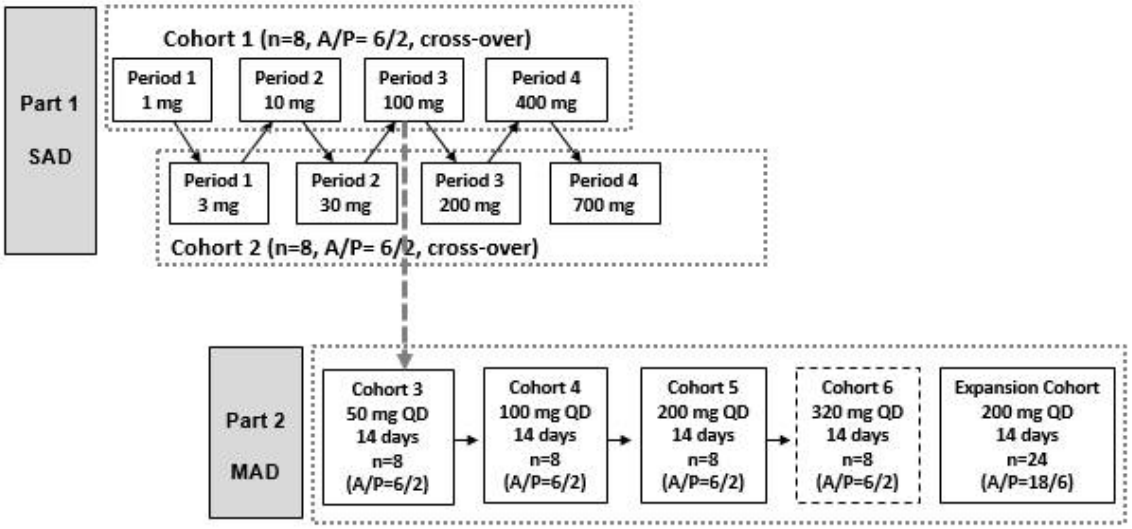
5.1 Figure 2 Phase 1 Study in Healthy Participants using planned doses of GSK3640254

PREVIOUS TEXT



Note: A=active, P=placebo. The doses shown here are intended to demonstrate general concepts relating to factors of escalation. X represents the predicted minimally efficacious dose. Y (in the expansion cohort alone) represents a dose previously studied in the multiple ascending dose (MAD) cohorts that did not meet the safety or PK stopping criteria. In Cohort 2 Period 4, a previous dose that was tolerated under fed conditions may be given under fasted conditions to assess food effect.

REVISED TEXT



Note: A=active, P=placebo. The doses shown here ~~are~~ **were/are being completed**. ~~intended to demonstrate general concepts relating to factors of escalation. X represents the predicted minimally efficacious dose. Y (in the expansion cohort alone) represents a dose previously studied in the multiple ascending dose (MAD) cohorts that did not meet the safety or PK stopping criteria. In Cohort 2 Period 4, a previous dose that was tolerated under fed conditions may be given under fasted conditions to assess food effect~~. **Amendment 04 proposes to evaluate a 320 mg Daily dose in MAD Cohort 6.**

Study Design Details Part 1 (SAD):

PREVIOUS TEXT

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts of eight healthy participants each. Each of these two cohorts will contain up to four escalating doses of GSK3640254. The interlocking design as shown in Figure 2 and the randomization sequence in Table will allow the 8 participants in each Cohort to potentially receive one of the two lowest and one of the two highest doses of GSK3640254. In each escalating period and Cohort, 6 participants will be randomized to GSK3640254 and 2 participants will be randomized to placebo. Details of the starting dose and dose escalation can be found in Section 5.5.3.

Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses (Table 2). Two participants in either Cohort will be assigned to one of the four treatment sequences, and each participant will receive placebo once.

Table 2 Description of treatment sequences in Cohort 1 and Cohort 2

REVISED TEXT

The SAD portion of the study will be conducted in an interlocking fashion with two separate cohorts of eight healthy participants each. Each of these two cohorts will contain up to four escalating doses of GSK3640254. The interlocking design as shown in Figure 2 and the randomization sequence in Table will allow the 8 participants in each Cohort to

potentially receive one of the two lowest and one of the two highest doses of GSK3640254. In each escalating period and Cohort, 6 participants will be randomized to GSK3640254 and 2 participants will be randomized to placebo. Details of the starting dose and dose escalation can be found in Section 5.5.3.

Participants in Cohort 1 and Cohort 2 will follow the same randomization strategy with alternating ascending doses (Table ~~2~~**5**). Two participants in either Cohort will be assigned to one of the four treatment sequences, and each participant will receive placebo once.

Table ~~2~~5 Description of treatment sequences in Cohort 1 and Cohort 2

Part 2 (MAD):

PREVIOUS TEXT

The earliest point at which Part 2 (MAD) of the study will be initiated is 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 GSK3640254, noted as X, is anticipated to be that which is predicted to provide a steady state Ctrough ≥ 0.11 μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1 (see Section 5.5.2 for further details). The initial dose in the MAD (Cohort 3) will be approximately half the anticipated minimally effective dose or 0.5X. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1).

Part 2 also includes an Expansion Cohort which will be conducted at the conclusion of the traditional MAD, once the evaluation of the safety and PK from Cohorts 3-6 is available. VH's prior and structurally similar MI (GSK3532795) ceased development in Phase 2b (due in part to a higher proportion of participants experiencing GI intolerability). GSK3532795, studied in Phase 1 studies of normal healthy volunteers showed diarrhoea of up to 65%. The Expansion Cohort will evaluate the rate of GI intolerability in 24 participants (active/PBO =18/6). The dose to be studied (Y) will be one of the previously studied doses in the MAD that did not meet the safety or PK stopping criteria. While no formal statistical testing will be performed, a summary of GI AEs will be provided from: 1) 24 participants receiving one of the GSK3640254 doses studied previously and 2) 14 participants receiving placebo across the entire MAD. These numbers of participants should provide sufficient clinical inference and better estimation of GI AEs frequency at a given dose (which can be used to inform subsequent dose selection/therapeutic index for HIV-1 infected participants).

REVISED TEXT

The earliest point at which Part 2 (MAD) of the study will be initiated is 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 GSK3640254, noted as X, is anticipated to be that which is predicted to provide a steady state Ctrough ≥ 0.11 μg/mL in 95% of participants and will be re-estimated based on the PK data collected in the early doses in Part 1 (see Section 5.5.2 for further details). The initial dose in the MAD (Cohort 3) will be approximately half the anticipated minimally effective dose or 0.5X. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed in the MAD until the anticipated steady-state exposure (Cmax and AUC(0-τ) on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the SAD portion of the study (Part 1). **However, as a plateau in exposure has been seen in the SAD between 400 mg and 700 mg, the highest dose in the MAD may be evaluating steady-state Cmax concentrations that are up to 50% greater than previously observed in the SAD while not exceeding AUC already explored in the SAD. The 320 mg QD dose Cmax on Day 14 will not exceed the SAD PK stopping criteria (see Section 8)**.

Part 2 also includes an Expansion Cohort which ~~will be~~ **was** conducted at the conclusion of ~~the traditional MAD~~ **Cohort 5.** ~~once the evaluation of the safety and PK from Cohorts 3-6 is available~~. VH's prior and structurally similar MI (GSK3532795) ceased development in Phase 2b (due in part to a higher proportion of participants experiencing GIintolerability). GSK3532795, studied in Phase 1 studies of normal healthy volunteers showed diarrhoea of up to 65%. The Expansion Cohort will evaluate the rate of GI intolerability in 24 participants (active/PBO =18/6). The dose ~~to be~~ studied (~~¥~~**200 mg**) ~~will be one of the~~ **was** previously studied doses in the MAD ~~that~~ **and** did not meet ~~the~~ safety or PK stopping criteria. While no formal statistical testing will be performed, a summary of GI AEs will be provided from: 1) 24 participants receiving one of the GSK3640254 doses studied previously and 2) 14 participants receiving placebo across the entire MAD. These numbers of participants should provide sufficient clinical inference and better estimation of GI AEs frequency at a given dose (which can be used to inform subsequent dose selection/therapeutic index for HIV-1 infected participants).

5.4 Scientific Rationale for Study Design

PREVOUS TEXT

In Part 2 of the study (MAD), doses potentially up to 4 times the minimally anticipated effective dose (X) are planned to be evaluated. In future studies in HIV-1-infected participants, these doses/exposures will be evaluated to understand the relationship between GSK3640254 exposures and efficacy, duration of response, and resistance development (see Section 5.5.2). Furthermore, assessment of this dose/exposure range (anticipated to be the therapeutic exposure range in the target population) in healthy participants will inform safety and tolerability prior to exposing a more vulnerable HIV-1-infected population to GSK3640254 and will inform risk mitigation strategies for potential drug interactions.

REVISED TEXT

In Part 2 of the study (MAD), doses potentially up to 4 times the minimally anticipated effective dose (~~X~~ ~ **80 mg QD**) are planned to be evaluated. In future studies in HIV-1-infected participants, these doses/exposures ~~will~~ **may** be evaluated to understand the relationship between GSK3640254 exposures and efficacy, duration of response, and resistance development (see Section 5.5.2). Furthermore, assessment of this dose/exposure range (anticipated to be the therapeutic exposure range in the target population) in healthy participants will inform safety and tolerability prior to exposing a more vulnerable HIV-1-infected population to GSK3640254 and will inform risk mitigation strategies for potential drug interactions.

5.5.1 Predicted Human Pharmacokinetics

PREVIOUS TEXT

The emerging PK data obtained at the three lower single doses of 1, 3 and 10 mg are presented in Section 3.2.2.

REVISED TEXT

The emerging PK data ~~obtained at the three lower single doses of 1, 3 and 10 mg~~ are presented in Section 3.2.2.

5.5.2 Predicted Human Effective Dose

PREVIOUS TEXT

The potential minimally effective dose for GSK3640254 was initially estimated using the predicted human PK profile, assuming similar between-participant PK variability to that observed with GSK3532795 (Population PK model based on data from Phase 2b study AI468038, Metrum Research Group, 2016), to ensure that 95% of participants have steady state trough concentrations that exceed the target concentration of 0.11 μg/mL following once daily dosing of GSK3640254. This led to the prediction of a likely minimally effective once daily dose of approximately 40 mg, assuming 58% bioavailability. Following single administration of 1, 3 and 10 mg of GSK3640254 in this study, a pharmacokinetic model was fit through the concentration-time data and these population PK parameters were used along with the previously assumed PK variabilities. The updated minimally effective once daily dose is approximately 70 mg. At this dose, the mean repeat-dose Cmax is predicted to be approximately 0.544 μg/mL, mean trough concentration is predicted to be approximately 0.238 μg/mL and mean AUC is predicted to be approximately 8.91 μg.h/mL (Table5). The anticipated steady-state mean AUC is 2.52-fold lower than the NOAEL in the rat, 6.86-fold lower than the LOAEL in the rat, and 8.23-fold lower than the LOAEL in the dog.

The relationship between GSK3640254 exposure and efficacy, duration of antiviral response, and development of on-treatment resistance will be evaluated in future studies in HIV-1-infected participants where assessment of a range of exposures will be important to inform the therapeutic dose range of GSK3640254. One exposure parameter of interest is inhibitory quotient (IQ), where IQ = Ctrough/PBA-EC_{90}. The IQs of other antiretrovirals at approved doses are approximately 19, 27, and 36 for dolutegravir 50 mg once daily, atazanavir 300 mg once daily with ritonavir, and lopinavir 400 mg twice daily with ritonavir, respectively [Van Lunzen, 2012 and Zhu, 2012]. For GSK360254, the minimally effective dose provides a trough concentration of 0.11 ug/mL at steady state in 95% of the participants and represents a geometric mean IQ of 7.92. To facilitate assessment of a range of GSK3640254 IQs in future studies in the target population, doses up to 4 times those of the minimally effective dose are planned for assessment in Part 2 (MAD) in healthy participants. These doses will be administered in accordance with PK and safety stopping criteria (see Section 8.1.3). Projected exposures at the highest anticipated once daily dose in the MAD include a mean repeat-dose Ctrough of 1.02 ug/mL and an IQ of 27.8.

REVISED TEXT

The potential minimally effective dose for GSK3640254 was initially estimated using the predicted human PK profile, assuming similar between-participant PK variability to that observed with GSK3532795 (Population PK model based on data from Phase 2b study AI468038, Metrum Research Group, 2016), to ensure that 95% of participants have steady state trough concentrations that exceed the target concentration of 0.11 μg/mL following once daily dosing of GSK3640254. This led to the prediction of a likely minimally effective once daily dose of approximately 40 mg, assuming 58% bioavailability. Following single administration of 1, 3 and 10 mg of GSK3640254 in this study, a pharmacokinetic model was fit through the concentration-time data and these population PK parameters were used along with the previously assumed PK variabilities. The updated minimally effective once daily dose ~~is~~ **was** approximately 70 mg. At this dose, the mean repeat-dose Cmax is predicted to be approximately 0.544 μg/mL, mean trough concentration is predicted to be approximately 0.238 μg/mL and mean AUC is predicted to be approximately 8.91 μg.h/mL (Table ~~5~~**8**). The anticipated steady-state mean AUC is 2.52-fold lower than the NOAEL in the rat, 6.86-fold lower than the LOAEL in the rat, and 8.23-fold lower than the LOAEL in the dog. **The population PK model was further updated with all the concentration-time data available up to 9 May 2018 (excluding the 700 mg SAD dose) and the population PK parameters including the between subject variabilities were used to provide the updated minimally effective once daily dose of approximately 80 mg.**

The relationship between GSK3640254 exposure and efficacy, duration of antiviral response, and development of on-treatment resistance will be evaluated in future studies in HIV-1-infected participants where assessment of a range of exposures will be important to inform the therapeutic dose range of GSK3640254. One exposure parameter of interest is inhibitory quotient (IQ), where IQ = Ctrough/PBA-EC_{90}. The IQs of other antiretrovirals at approved doses are approximately 19, 27, and 36 for dolutegravir 50 mg once daily, atazanavir 300 mg once daily with ritonavir, and lopinavir 400 mg twice daily with ritonavir, respectively [Van Lunzen, 2012 and Zhu, 2012]. For GSK36**4**0254, the

minimally effective dose provides a trough concentration of 0.11 ug/mL at steady state in 95% of the participants and represents a geometric mean IQ of 7.92. To facilitate assessment of a range of GSK3640254 IQs in future studies in the target population, doses up to 4 times those of the minimally effective dose are planned for assessment in Part 2 (MAD) in healthy participants. These doses will be administered in accordance with PK and safety stopping criteria (see Section 8.1.3). Projected exposures at the highest anticipated once daily dose in the MAD include a mean repeat-dose Ctrough of 1.02 ug/mL and an IQ of 27.8.

5.5.3. Part 1 (SAD) Starting Dose and Dose Escalation

PREVIOUS TEXT

Table 3 Probability of any SAD participant (Cmax >7.96 µg/mL) for potential doses

REVISED TEXT

Table ~~3~~6 Probability of any SAD participant (Cmax >7.96 µg/mL) for potential doses

5.5.4 Part 2 (MAD) Starting Dose and Dose Escalation

PREVIOUS TEXT

The initial dose in the MAD (Cohort 3) will be approximately half the likely minimally effective dose, re-estimated based on the clinical PK data collected in the early doses of Part 1. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts, and will be governed by both safety and MAD PK stopping criteria (see Section 8.1.3 and Section 8.1.4). Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any participant AUCtau in the MAD above 61.1 µg.hr/mL, the MAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table 4.

Table 15 Probability of any MAD participant (AUCtau > 61.1 µg.h/mL) for potential QD doses

REVISED TEXT

The initial dose in the MAD (Cohort 3) will be approximately half the likely minimally effective dose, re-estimated based on the clinical PK data collected in the early doses of Part 1. Dose escalation in the MAD will not exceed approximately 2-fold between cohorts, and will be governed by both safety and MAD PK stopping criteria (see Section 8.1.3 and Section 8.1.4). Given different assumptions for the between participant AUC variability (%CVb) and the current human PK prediction, the probability of any

participant AUCtau in the MAD above 61.1 µg.hr/mL, the MAD PK Stopping Criterion (Section 8.1.3), are illustrated in Table ~~71~~.

Table ~~16~~7 Probability of any MAD participant (AUCtau > 61.1 µg.h/mL) for potential QD doses

5.5.6. Anticipated Exposure and Safety Cover for a Range of Potential Doses

PREVIOUS TEXT

Projected steady-state exposures of GSK3640254 from potential doses in Part 2, taking into consideration the PK emerging from single doses of 1, 3 and 10 mg, are compared to target efficacious concentrations and preclinical toxicity exposures in Table5. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats and only to a LOAEL in dogs. Findings in both species were GI related, limited and reversible (see Section 3.3.1 and the CIB for details).

Table 17 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

REVISED TEXT

Projected steady-state exposures of GSK3640254 from potential doses in Part 2, taking into consideration the PK emerging from single doses of 1, 3 and 10 mg, are compared to target efficacious concentrations and preclinical toxicity exposures in Table ~~582~~**8**. Predicted human exposure following multiple doses can be compared to the NOAEL and LOAEL in rats and only to a LOAEL in dogs. Findings in both species were GI related, limited and reversible (see Section 3.3.1 and the CIB for details).

Table ~~18~~8 Projected steady-state PK for a range of potential QD doses following fed administration and comparison to efficacy target and preclinical exposure

9.4.3.2. Cardiodynamic assessment (ECGs extracted from Holter recordings)

High-Precision QT Analysis

PREVIOUS TEXT

Categorical T-wave morphology analysis (Table 6) and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

Table 19 T-wave morphology categories (assessed manually)

REVISED TEXT

Categorical T-wave morphology analysis (Table ~~6~~**9**) and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

Table ~~20~~9 T-wave morphology categories (assessed manually)

9.4.6. GI Toxicity Evaluation and Management

PREVIOUS TEXT

Pre-clinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254. This section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table 7). The Investigator may contact the GSK/VH Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table 21 GI Toxicity Evaluation and Management

REVISED TEXT

Pre-clinical toxicology studies in rats and dogs have suggested a potential for GI related toxicity with GSK3640254. This section provides general guidance to the Investigator on the evaluation and management of primarily upper gastrointestinal symptoms (Table ~~7~~ **10**). The Investigator may contact the GSK/VH Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the trial.

Table ~~22~~10 GI Toxicity Evaluation and Management

10.3.3. Interim Analyses

Bayesian model Operating Characteristics (OC)

PREVIOUS TEXT

For each trial, the Bayesian probability for the 700mg dose is calculated and compared with different thresholds (40%, 50% or 60%). Among those 1000 trials, the percentages of trials with Bayesian probability below the thresholds, which stands for the percentage of trials that could be escalated to dose 700mg, are listed in Table 115.

Table 23 Percentage of trials with Bayesian probability less than the threshold (40%, 50% or 60%)

REVISED TEXT

For each trial, the Bayesian probability for the 700mg dose is calculated and compared with different thresholds (40%, 50% or 60%). Among those 1000 trials, the percentages of trials with Bayesian probability below the thresholds, which stands for the percentage of trials that could be escalated to dose 700mg, are listed in Table ~~8~~**11** .

Table ~~2~~411 Percentage of trials with Bayesian probability less than the threshold (40%, 50% or 60%)