Protocol: Bioequivalence of Crushed and Whole Genvoya Tablets (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate) _____

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Study Site: Johns Hopkins University

Study Sponsor: Gilead Sciences, Inc.

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SCHEMA

Rationale	Genvoya, a once-daily single fixed-dose combination tablet for treatment of HIV-infection, consists of two nucleoside reverse transcriptase inhibitors (NRTIs), emtricitabine (FTC) and tenofovir (TFV) alafenamide fumarate (TAF), the integrase strand transfer inhibitor (InSTI) elvitegravir (EVG), and the boosting agent cobicistat (COBI). It is unknown whether Genvoya, taken as a crushed/dissolved tablet, is bioequivalent to when taken as a whole tablet. This is crucial information since a substantial number of HIV-infected individuals suffer from pill aversion that could lead to non-adherence and treatment failure.
Design	Within-subject, fixed-order, two-period, open label study to determine the bioequivalence of oral single dose of whole and crushed/dissolved tablets of *Genvoya* in healthy adult male and female research participants administered under direct observation.
Population	Up to 20 adult male and female healthy research participants will be enrolled to complete 12.
Intervention	Whole Tablet Period: Single observed oral dose of Genvoya **whole** tablet Crushed/dissolved Tablet Period: Single observed oral dose of Genvoya crushed/dissolved tablet
Outcome Measures	Primary: To investigate the bioequivalence of oral single whole tablet and crushed/dissolved tablet of Genvoya by characterizing the plasma $AUC_{0-\infty}$ and C_{max} of EVG, COBI, FTA, TAF, and TFV in plasma, after single doses of whole tablet and crushed/dissolved tablet in healthy male and female adult research participants. Secondary: To compare other pharmacokinetic parameters of oral single whole tablet and crushed/dissolved tablet of Genvoya by characterizing the plasma T_{max} and terminal elimination half-life of EVG, COBI, FTA, TAF, and TFV after single doses of whole tablet and crushed/dissolved tablet in healthy male and female adult research participant.
Procedures	Screening: Potential research participants provide written informed consent and undergo evaluation of inclusion and exclusion criteria. Whole Tablet Period (3 days): Research participants will swallow, under direct observation, a single dose of a whole Genvoya tablet, followed by plasma sampling for 72 hours as indicated in **Table 1** below. Safety Visit: Participants will return approximately 7 days after the whole-tablet dosing for clinical and laboratory safety assessment visit. Washout: A minimum of 14 will elapse between the two Genvoya doses. Crushed/dissolved Tablet Period (3 days): Research participants will swallow, under direct observation, a single dose of a crushed/dissolved Genvoya tablet, followed by plasma sampling for 72 hours, as indicated in **Table** 1 below. Final Safety Visit: Participants will return approximately 7 days after the crushed/dissolved-tablet dosing for a final clinical and laboratory safety assessment visit. * Adverse events will be monitored at all study visits and graded using the DAIDS Adverse Events Grading Table (Version 2.1, July 2017) as outlined in the protocol.

Table 1: Pharmacokinetic Sampling Schedule

Sampling Hour	Pre-dose	0.25	0.5	0.75	1.0	1.5	2	3	4	5	6	10	14	24	48	72
EVG	x				x		x	x	x	x	x	x	x	x	x	x
COBI	x		x		x		x	x	x		x	x	x	x	x	
FTC	x		x		x		x	x	x		x	x	x	x	x	x
TAF	x	x	x	x	x	x	x	x	x		x					
TFV	x	x	x	x	x	x	x	x	x		x	x		x	x	x

1 INTRODUCTION

1.1 Background

Genvoya, a fixed-dose combination of the two non-nucleosides reverse transcriptase inhibitors (NRTIs) emtricitabine (FTC) and tenofovir (TFV) alafenamide fumarate (TAF), with the integrase strand transfer inhibitor (InSTI) elvitegravir (EVG) and the EVG-boosting agent cobicistat (COBI), is FDA approved for the treatment of HIV-infected patients (1).

Despite the availability of Genvoya, allowing for a single tablet fixed-dose combination and once-daily dosing, a substantial number of individuals living with HIV suffer from pill aversion, dysphagia, odynophagia, or problems swallowing their oral regimens - all of which can contribute to non-adherence (2). These observations are especially important because non-adherence to antiretroviral (ARV) medications is highly prevalent and associated with decreased survival (3). Non-adherence has been estimated at 55% in North American pooled cohorts, and is a vital public health concern, as it leads to treatment failure and transmission of drug-resistant virus (4-6).

Many clinical scenarios make the administration of crushed/dissolved tablets desirable as a potential strategy to overcome pill aversion. However, there is a theoretical concern that the systemic absorption of the active ingredients of tablets may be altered by crushing the pills. In fact, pharmacokinetic and bioequivalence data are lacking for most ARV fixed-dose combinations used in the treatment of HIV-infected patients. It is therefore of substantial practical and clinical interest to know whether ARV combinations such as Genvoya can be taken in crushed/dissolved form with bioequivalence to whole tablet form.

A recent study reported the bioavailability results from crushing and splitting the single fixed-dose formulation tablet containing darunavir (DRV), cobicistat (COBI), emtricitabine (FTC), and TAF (7). This was an open-label, randomized, cross-over study in 30 HIV healthy research participants, using a single dose of this fixed dose formulation as whole tablet, crushed/dissolved tablet, and halved tablet. Plasma concentrations for each method of administration were comparable for DRV, FTC, and COBI. Although TAF was bioequivalent for the whole versus split tablet, the crushed/dissolved tablet resulted in 20% reduced TAF AUC. Therefore, further studies are needed to confirm these results. Also, it is crucial to conduct a bioequivalence study with the Genvoya tablet, since this fixed-dose formulation includes EVG, a different ARV class than DRV in the previous bioavailability study (7).

The national treatment guidelines recommend that treatment-naive HIV-infected patients receive an initial combination regimen with InSTI-based therapy (8). Thus, InSTIs are a relevant class of ARV drugs for the treatment of HIV infection, and showing whether these medications can be taken in a crushed/dissolved tablet form can be a lifesaving intervention for individuals who cannot tolerate ingesting a whole tablet formulation.

In this short pharmacokinetic study we will investigate whether an oral single-dose of whole tablets of Genvoya is bioequivalent to a crushed/dissolved form of this medication in healthy research participants.

1.2 STUDY DRUGS: CLINICAL PHARMACOLOGY AND SAFETY

Genvoya (EVG/COBI/FTC/TAF)

Genvoya is a once-daily single fixed-dose combination tablet for treatment of HIV-infection. One tablet consists of two NRTIs, FTC 200 mg and TAF 10 mg, the InSTI EVG 150 mg, and the EVG-boosting agent COBI 150 mg (1). The FDA recommended dosage of Genvoya in patients ≥12 years old is one tablet daily taken with food (1). Genvoya should not be used in patients with a creatinine clearance (CrCl) <30 mL/min (1). EVG and COBI are highly bound to plasma proteins (1).

Safety. The most common adverse effects with Genvoya are diarrhea, nausea, fatigue, and headaches (1). Most of these adverse events are self-limited and resolve spontaneously. COBI is known to inhibit creatinine secretion that leads to an increase in serum creatinine, and a corresponding reduction in GFR and creatinine clearance although actual GFR is not affected (1). In addition, more patients treated with Genvoya had LDL levels >190 mg/dL compared to Stribild*,* 5% and 2%, respectively (1).

Cardiac electrophysiology studies showed that EVG and TAF did not prolong or affect the PR and QT/QTc intervals, respectively, while COBI prolonged the PR interval in one study (1). However, the dose of COBI in the Genvoya tablet is lower than doses evaluated in cardiac electrophysiology study. Therefore, it is unlikely that treatment with Genvoya will lead to clinically important prolongation of the PR interval (1). The effect of the combination regimen Genvoya or FTC on the QT interval is unknown. Genvoya has been giving to healthy research participants in a number of studies with minimal reported toxicity (1). It is also important to underscore that most of the side effects associated with Genvoya occur with chronic use of this ARV medication and, thus, less likely to occur with the short-term term dosing proposed in this bioavailability study.

Genvoya is a category B drug for use during pregnancy (1). No adverse developmental effects were observed in animal studies when the components of Genvoya were administered separately during the period of organogenesis (1). TAF use in women during pregnancy has not been evaluated, while EVG, COBI, and FTC use during pregnancy has been evaluated in a limited number of women (1). Current data showed no birth defects reported for COBI or EVG and no difference in the overall risk of major birth defects for FTC compared with a U.S. reference population (1). It is unknown if COBI, EVG, and TAF are present in human breast milk; FTC has been shown to be present in human breast milk (1).

Clinical Pharmacology. The PK parameters of individual components of Genvoya are listed in **Table 2**. All PK parameter data are taken from the Genvoya™ package insert for EVF, COBI, FTC, and TAF. Data for TFV, which results from the conversion of TAF, is taken from the Vemlidy™ package insert with adjustment of PK parameters for 10 mg dose of TAF in Genvoya vs. 25 mg in Vemlidy, assuming dose proportionality (C_{max}, $AUC_{0-\infty}$, and C_{trough}) and the Genvoya package insert (TFV half-life only which differs significantly from TFV half-life when administered as TDF).

Table 2. Summary of Genvoya constituent drugs pharmacokinetic parameters after oral administration in HIV-infected adults. Mean (SD).

Parameter	Units	EVG	COBI	FTC	TAF	TFV (from TAF)
Dose	mg	150	150	200	10	NA
C_{max}	mg/mL	1.7 (0.4)	1.1 (0.4)	1.9 (0.5)	0.16 (0.08)	0.012
$AUC_{0-\infty}$	mg/hr/mL	23.0 (7.5)	8.3 (3.8)	12.7 (4.5)	0.21 (0.15)	0.16
C_{trough}	mg/mL	0.45 (0.26)	0.05 (0.13)	0.14 (0.25)	NA	0.04
Half-life	hours	12.9	3.5	10	0.51	32

COBI and EVG are metabolized by CYP3A4 enzyme; therefore, concomitant use of these two drugs with CYP3A4 inhibitors could substantially increase their plasma concentration (1). COBI is also metabolized by CYP2D6. CYP3A4 inducers on the other hand, lower COBI and EVG plasma concentrations which may lead to loss of therapeutic effect of Genvoya and development of treatment failure and viral resistance (1). COBI is also an inhibitor of CYP3A4 and CYP2D6 in addition to drug transporters such as breast cancer resistance protein (BCRP), p-glycoprotein (P-gp), and organic anion transporting peptide (OATP) 1B1 and 1B3 (1). Therefore, co-administration of Genvoya with CYP3A4, CYP2D6, P-gp, BCRP, OATP1B1 or OATP1B3 substrates can significantly increase their plasma concentrations.

EVG, a CYP2C9 inducer, can lower plasma concentrations of substrates metabolized through this pathway (1). TAF is a weak inhibitor of CYP3A *in vitro* but not an inhibitor or inducer of CYP3A *in vivo;* TAF is also a substrate of P-gp, BCRP, OATP1B1 and OATP1B3 (1). Therefore, inhibitors of these drug transporters may increase the absorption of TAF. Conversely, drugs that induce the activity of these drug transporters could lead to a reduction TAF absorption and decrease TAF plasma concentrations (1). FTC is renally eliminated and does not undergo biotransformation through the cytochrome P450 pathway (1). Coadministration of Genvoya with drugs that can affect renal function can lead to a reduction of renal elimination of FTC and consequently an increase in FTC concentrations and potential adverse events. Other mechanism of drug interactions with the components of Genvoya besides drug transporters and hepatic drug metabolizing enzymes, include diminished absorption when EVG is coadministered with drugs containing polyvalent cations (e.g., Mg, Al, Fe, or Ca; 1).

2 RATIONALE

Despite the availability of Genvoya, a single tablet once-daily fixed-dose formulation, a substantial number of individuals living with HIV infection still have difficulty swallowing whole tablets of ARV combinations. Therefore, crushed/dissolved tablet oral formulations are highly desirable as a potential strategy to overcome pill aversion. However, there is a theoretical concern that the systemic absorption of the active ingredients of the whole tablet formulation may be altered by crushing the tablets. We propose a study in healthy adult women and men research participants to determine whether Genvoya in crushed/dissolved form is bioequivalent with the whole tablet form.

The FDA recommended dosage of Genvoya is one tablet daily for the treatment of HIV infection (1). Since participants in this bioequivalence study will be dosed with Genvoya for only one dose on two occasions, we will only enroll healthy HIV-uninfected individuals in order to prevent the development of potential

viral resistance that could occur with this short-term drug exposure. In addition, healthy research participants are less likely to be using other medications that could affect the metabolism, absorption or elimination of the components of Genvoya and consequently interfere with the proposed study endpoints.

Genvoya was selected for this bioavailability study because this fixed combination InSTI-based therapy is included in the national treatment guidelines as a first line therapy for the treatment of HIV infection (8). Therefore, Genvoya is frequently prescribed for treatment-naïve patients initiating ART.

3 HYPOTHESIS and STUDY OBJECTIVE

3.1 Hypothesis

3.1.2 Genvoya crushed/dissolved tablet will be bioequivalent to the whole tablet.

3.2. Primary Objective

3.2.1 To investigate the bioequivalence of oral single whole tablet and crushed/dissolved tablet of Genvoya in healthy research participants by characterizing the plasma $AUC_{0-\infty}$ and C_{max} of EVG, COBI, FTC, TAV, and TFV after single doses of a whole and crushed/dissolved tablet of this fixed-dose ARV combination in healthy adult research participants.

3.3 Secondary Objective

3.3.1 To compare other pharmacokinetic parameters of oral single whole tablet and crushed/dissolved tablet of Genvoya in healthy adult research participants, T_{max}, and terminal elimination half-life, in plasma of EVG, COBI, FTC, TAF, and TFV.

4 STUDY DESIGN

The proposed bioequivalence study will have two pharmacokinetic observation periods:

Whole Tablet Period: Research participants will be asked to swallow a single whole Genvoya tablet under direct observation. The first 72-hour pharmacokinetic sampling period for each of the ARV components of Genvoya will occur as outlined in **Table 3**. Participants will return for a safety visit for clinical and laboratory assessments seven days after whole tablet dosing. A minimum 14 day washout period will take place between the whole tablet dosing and the crushed/dissolved tablet dosing.

Crushed/Dissolved Tablet Period: Research participants will be asked to swallow a single crushed/dissolved Genvoya tablet under direct observation. The second and final Genvoya pharmacokinetic sampling will occur as outlined in **Table 3**.

Pharmacokinetic Sampling. Plasma sampling for estimating pharmacokinetic parameters were selected to optimize information content of each sample for each drug (and TFV metabolite of TAF) for robust estimates of T_{max}, C_{max}, $AUC_{0-\infty}$, and terminal elimination half-life. These are based on prior observations of T_{max} and half-life.

Table 3. Pharmacokinetic sampling schedule

Sampling Hour	Pre-dose	0.25	0.5	0.75	1.0	1.5	2	3	4	5	6	10	14	24	48	72
EVG	x				x		x	x	x	x	x	x	x	x	x	x
COBI	x		x		x		x	x	x		x	x	x	x	x	
FTC	x		x		x		x	x	x		x	x	x	x	x	x
TAF	x	x	x	x	x	x	x	x	x		x					
TFV	x	x	x	x	x	x	x	x	x		x	x		x	x	x

The proposed pharmacokinetic sampling visits will be conducted at the Drug Development Unit (DDU) in the Division of Clinical Pharmacology at the Johns Hopkins Hospital. The DDU staff has extensive experience conducting pharmacokinetic studies in healthy research participants. The DDU will provide study coordinators and other administrative research support, and recruit participants for this study.

Plasma samples will be processed and analyzed at the Clinical Pharmacology Analytical Laboratory (CPAL) within the Division of Clinical Pharmacology. Genvoya tablets will be donated by Gilead and will be stored and dispensed by the Johns Hopkins Investigational Pharmacy. Approximately 8ml of blood will be collected in each dosing period, on the time points outlined in **Table 3**. The plasma concentrations of EVG, COBI, FTC TFV, and TAF will be quantified using validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods (UPLC-MS/MS). Assay validation reports are peer-reviewed and approved by the DAIDS-sponsored Clinical Pharmacology Quality Assurance program.

Safety Assessments. Safety will be assessed by monitoring physical examinations, vital signs, and laboratory and clinical adverse events. Safety laboratory tests will be performed at the two safety visits post dose with whole and crushed/dissolved Genvoya tablets. Laboratory tests will include hematology and chemistry. A negative HIV-1/2 Antigen/Antibody (Ag/Ab) screening test and negative hepatitis B surface antigen test in addition to chemistry, and hematology results as specified in the inclusion criteria section are required to meet study eligibility criteria.

5 STUDY DRUGS, ADMINISTRATION AND DURATION

The protocol-specified ARV regimens are:

- Whole Tablet Period: Single observed oral dose of Genvoya whole tablet (EVG 150mg/COBI 150mg/FTC 200mg/TAF 10mg) under direct observation.

- Crushed/Dissolved Tablet Period: Single observed oral dose of Genvoya crushed/dissolved tablet (EVG 150mg/COBI 150mg/FTC 200mg/TAF 10mg) under direct observation.

Genvoya will be administered with a light meal. Crushed/dissolved Genvoya tablet solution will be

prepared at the Johns Hopkins Investigational Pharmacy.

Genvoya tablets will be donated by Gilead Sciences and will be dispensed by the Johns Hopkins Investigational Pharmacy. The Johns Hopkins Investigational Pharmacy will also maintain complete records of all study medications. All unused study medications must be returned to the Johns Hopkins Investigational Pharmacy after the study is completed or terminated. Unused or returned study medications will be destroyed.

6 STUDY POPULATION

Up to twenty male and female health research participants will be enrolled in this study to assure twelve individuals complete the trial. All participants will meet inclusion/exclusion criteria as outlined in this protocol. Healthy research participants will be recruited by the Johns Hopkins DDU staff.

7 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

7.1 Inclusion Criteria

7.1.1 Healthy adults ≥18 years of age.
7.1.2 Negative HIV-1/2 Ag/Ab serology documented within 30 days prior to study entry.
7.1.3 Negative Hepatitis B surface antigen within 30 days prior to study entry.
7.1.4 Ability and willingness of subject to provide a signed informed consent and comply with study requirements.
7.1.5 Negative POCT qualitative urine pregnancy test (female participants only).
7.1.6 All subjects must not participate purposely in a conception process (e.g., active attempt to impregnate, sperm donation, or in vitro fertilization). If participating in sexual activity that could lead to pregnancy subjects must take every precaution to avoid risk of pregnancy by using a reliable contraception for the duration of the study therapy (e.g., condoms, hormonal, barrier).
7.1.7 Laboratory values and physical examination as judged by the principal investigator to be safe to participate including normal renal function.
7.1.8 Good peripheral venous access for proposed pharmacokinetic sampling.
7.1.9 Willingness and ability to take oral medications.

7.2 Exclusion Criteria

7.2.1 History of chronic or acute medical conditions that in the opinion of the investigator would jeopardize safety of subjects participating in this study.
7.2.2 Known or suspected hypersensitivity to the components of Genvoya.
7.2.3 Currently taking or having taken oral PrEP or PEP (e.g. Truvada®) within 30 days of study entry, or anticipated use of PrEP/PEP during study participation
7.2.4 Use of prescription or over-the-counter medications, including agents containing polyvalent cations (e.g., Mg, Al, Fe, or Ca), or any other drugs that in the opinion of the investigator could interfere with the pharmacokinetics of any of the ARV components of Genvoya within 2 weeks prior to either study dose.
7.2.5 Pregnant or breast feeding.

7.2.6 Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
7.2.7 Hospitalization or therapy for serious illness within 30 days prior to study entry as judged by the investigator.
7.2.8 Participation in any investigational drug study within 30 days prior to study entry that in the opinion of the investigator would preclude study participation.
7.2.9 Taking any medication listed in the package insert that is contraindicated with Genvoya.
7.2.10 Any other condition or prior therapy that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, make the individual unsuitable for the study or unable to comply with the study requirements. Such conditions may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled substance abuse, or renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease.

8 CONCOMITANT AND PROHIBITED MEDICATIONS

Use of any licensed drugs during the study is prohibited unless medically required for the safety of the subjects, and requires prior approval by the study investigators. If a concomitant medication is needed and approved by the study investigators, the package insert will be reviewed to ensure that the team has the most current information on drug interactions. Concomitant use of herbals, dietary supplements, nutritional supplements, or any other complementary and alternative medicine compounds containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) is not allowed from the 14 days prior to, and 3 days following each study dose. Investigational medications are also prohibited.

9 CLINICAL AND LABORATORY EVALUATIONS

Study Schedule

The study visits are described below as to their timing, procedures, and sample collections and summarized in **Table 3** Schedule of Events.

9.2 Definitions for Study Schedule

9.2.1 Screening (Visit 1)

Screening will be scheduled at the Johns Hopkins DDU and must occur prior to the subject taking any study medication. At the beginning of the screening visit, subjects will be asked to read and sign the informed consent approved by the Johns Hopkins IRB, and will undergo screening laboratory and clinical evaluation. Eligibility of study participation will be determined by screening evaluations. Screening evaluations to determine eligibility must be completed within 30 days prior to study entry and administration of study drugs.

The following assessment and procedures will be performed at screening visit:

- Medical/Medications history
- Physical examination (including vital signs, weight and height)

- HIV-1/2 Ag/Ab serology and Hepatitis B surface antigen testing
- POCT qualitative urine pregnancy test (female participants only)
- CBC with differential
- Complete Metabolic Panel (sodium, potassium, chloride, carbon dioxide, glucose, urea nitrogen, creatinine, calcium, total protein albumin, total bilirubin, alkaline phosphatase, AST, ALT)
- Serum Phosphorus
- Estimated creatinine clearance (Cockcroft-Gault Formula)

Medical history should include current or recent use of illicit drugs, alcohol, and tobacco; any prescription medications within the last 30 days; all diagnoses active within the preceding 30 days; past medical history; and current contraception method if participants are engaging in sexual activity.

The medication history should consist of the following: all prescription, nonprescription medications, alternative therapies, vitamins and dietary supplements taken within 30 days of entry, including actual or estimated start and stop dates. Following entry, all prescription and nonprescription medications taken since the last clinic visit should be recorded.

Weight will be measured and recorded on the source document at screening to calculate creatinine clearance at entry, at each dosing visit, and at the final safety visit. Height will be measured and recorded once at screening.

Blood pressure, temperature, and pulse rate will be collected at all visits and recorded on the source documents.

Complete physical examination is required at screening. The complete physical exam does not include genital, breast, and rectal examinations.

9.2.2 Day 1 (Visits 2 and 7) Genvoya Dosing Under Direct Observation followed by pharmacokinetic sampling.

Participants who satisfy the inclusion criteria will be asked to return to the DDU on Day 1. Individuals will be given a single oral dose of Genvoya whole tablet (Whole Tablet Period) or a crushed/dissolved Genvoya tablet mixed in water (crushed/dissolved Tablet Period) under direct observation. They will undergo pharmacokinetic sampling at the DDU for the components of Genvoya as outlined in **Table 2** (Pharmacokinetic sampling schedule) and **Table 3** (Schedule of Events). Approximately 8 mL will be collected at all pharmacokinetic time points. Serum creatinine will be collected once, pre-dose, for estimated creatinine clearance. Female participants will have a POCT qualitative urine pregnancy test prior to dosing and negative test results are required for participants to continue with dosing/the study visit. Any positive POCT qualitative urine pregnancy test results will be confirmed with a serum quantitative pregnancy test.

At entry, all signs, symptoms, and diagnoses within 30 days prior to entry will be recorded, including actual and estimated dates of onset and resolution. After entry, all new diagnoses,

signs and symptoms will be recorded at the visit they are reported and should include status, date of onsent, date of discovery and date of resolution, if applicable.

For the WholeTablet Period, subjects will be given a single oral dose of a whole Genvoya tablet under direct observation. Participants will be asked to return to the DDU approximately 7 days after receiving the whole tablet dose, in order to complete the first study safety evaluation. Participants will be required to undergo a minimum 14-day washout period following receipt of the Genvoya whole tablet.

For the Crushed/Dissolved Tablet Period, subjects will be given a single oral dose of a crushed/dissolved Genvoya tablet under direct observation. The solution of crushed/dissolved Genvoya tabled mixed in water will be prepared at the Johns Hopkins Investigational Drug Pharmacy. Participants will be asked to return to the DDU approximately 7 days after receiving the crushed/dissolved tablet dose, in order to complete the final study safety evaluation.

Table 3. Schedule of Events

Evaluations	[1]Screening	Whole Tablet Period[2]				Safety Visit	Crushed/Dissolved Tablet Period[2]				Safety Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Day -30	Day 1	Day 2	Day 3	Day 4	Day 8	Day 1	Day 2	Day 3	Day 4	Day 8
Informed Consent	X										
Vital Signs (BP, HR, Temp)	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X				X
Height	X										
HIV-1/2 Ag/Ab	X										
HBsAg	X										
CBC w/ Diff	X										X
Complete Metabolic Panel	X	X[2]				X	X[2]				X
Serum Phosphorus	X					X					X
POCT Qualitative Urine HCG (female participants only)	X	X					X				
[3]Estimated Creatinine Clearance	X	X					X				X
Medical /Medication History	X										
Physical Exam	X										
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam[4]		X	X	X	X	X	X	X	X	X	X
Observed whole dose Genvoya		X									
Observed crushed/dissolved dose Genvoya							X				
Plasma Pharmacokinetics[5]		X	X	X	X		X	X	X	X	

[1]Screening within 30 days of entry

[2]Serum creatinine only

[3]Creatinine Clearance estimated by Cockcroft-Gault formula

[4]A targeted physical exam will only be completed if clinically indicated

[5]Pharmacokinetic sampling time points pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 10, 14, 24, 48, and 72 hours after each dose. There is a +/- 5 min window for 0.25hr to 1.5hr PK specimen collection and a +/- 15 min window for 2hr to 14hr PK specimen collection. Windows for 24, 48 and 72 hr PK specimen collection outlined in section 9.2.3-9.2.5.

9.2.3 Day 2 (Visits 3 and 8) – 24 hour PK sampling

Participants will return to the clinic for a 24 $\pm$ 1 hour pharmacokinetic blood sample. They will be asked about any new or continuing adverse events and concomitant medications. A targeted physical examination will be performed if any adverse event is reported.

9.2.4 Day 3 (Visits 4 and 9) – 48 hour PK sampling

Participants will return to the clinic for a 48 $\pm$ 2 hours pharmacokinetic blood sample. They will be asked about any new or continuing adverse events and concomitant medications. A targeted physical examination will be performed if any adverse event is reported.

9.2.5 Day 4 (Visits 5 and 10) – 72 hour PK sampling

Participants will return to the clinic for a 72 $\pm$ 4 hours pharmacokinetic blood sample. They will be asked about any new or continuing adverse events and concomitant medications. A targeted physical examination will be performed if any adverse event is reported.

9.2.6 Day 8 (Visits 6 and 11) - Safety Visit

Subjects will return to the DDU 7 days $\pm$ 3 days following the direct observed dose of Genvoya for a safety study visit. Subjects will undergo clinical and laboratory evaluations as outlined in the schedule of events. A targeted physical examination is to be driven by any signs or symptoms previously identified that the subject has experienced since the last visit, or newly occurring that the subject has experienced since the previous visit. A targeted physical examination is not necessary if the subject does not have new symptoms. In the absence of new symptoms, a target physical examination may still be require to document resolution of previous findings on physical examination.

Study subjects will be reminded that they must not participate in a conception process. Participants will also be advised regarding HIV prevention during the study.

Adverse events will be monitored throughout the study according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Participants experiencing grade $\geq$3 toxicity that is deemed by the investigator as associated with Genvoya will be discontinued from the study. These subjects will be followed until resolution, return to baseline values, stabilization, or an adequate explanation can be given for their condition. They will complete the last safety evaluation visit outlined in the schedule of events. Patients experiencing grades 1 or 2 toxicity will continue in the study at the discretion of the investigator.

At visit 6, participants will be scheduled to return to the DDU to start the Crushed/Dissolved Tablet Period of the study.

The final safety evaluation visit is also the premature study drug discontinuation visit. They will undergo clinical and laboratory assessments as outlined in the schedule of events.

9.2.7 Evaluations for Subjects Who Do Not Start Study Drugs

No follow up evaluations are required for study subjects who do not start study drugs.

9.2.8 Completion of Protocol

A subject is considered to have completed the study if he/she completed the two study periods for whole and crushed/dissolved Genvoya plasma pharmacokinetic sampling.

9.2.9 Study Drug Modifications

Dose modifications/reductions/interruptions of study medications to manage toxicity are not allowed in this study. Subjects requiring dose modifications/reductions/interruptions for the management of toxicities at any time during the study will be taken off study.

10 TOXICITY MANAGEMENT

Dose modifications/reductions/interruptions of study medications to manage toxicity are not allowed in this study. Subjects requiring dose modifications/reductions/interruptions for the management of toxicities at any time during the study will be taken off study and complete the safety evaluation. Adverse events will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

- Grade 1 Toxicities

For all Grade 1 toxicities study participants may continue on study at the discretion of the study investigator and will be followed carefully.

- Grade 2 Toxicities

For all Grade 2 toxicities the participant may continue on study at the discretion of the site investigator.

- Grade ≥3 Toxicity

If a participant has a Grade 3 or greater toxicity attributed to the study drug, the participant will not receive any further Genvoya dosing. These individuals will be followed until resolution, stabilization, return to baseline values or an adequate explanation can be given for their condition. They will complete the evaluations scheduled for the safety visit. Additional clinic visits and evaluations might be necessary as medically indicated.

11 CRITERIA FOR DISCONTINUING FURTHER GENVOYA DOSING

- Requirement of concomitant medication that is judged by the site investigator to interfere with study continuation.
- Request by the subject to withdraw.
- Clinical reasons believed life threatening by the investigator, even if not addressed in the toxicity management of the protocol.
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- Drug toxicity as defined in Section 10.
- At the discretion of the investigator, regulatory agencies, or pharmaceutical sponsor.
- Failure by the subject to take study medications as instructed.
- Failure to complete a pharmacokinetic sampling visit within the allowable timeframe.

12 CRITERIA FOR PREMATURE STUDY DISCONTINUATION

- Request by the study subjects to withdraw.
- Drug toxicity as defined in Section 10.
- Request of the primary care provider if s/he is no longer in the best interest of the subject.
- Subject judged by the investigator to be at significant risk for falling to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- Imprisonment or the compulsory detention for treatment of either psychiatric or physical illness.
- At the discretion of the investigator, regulatory agencies, or pharmaceutical sponsor.
- Toxicities as outlined in Section 10 of the protocol.

13 STATISTICAL CONSIDERATIONS

An equivalence approach with no-effect boundaries of 80 to 125% will be employed, in accordance with the FDA guidance on bioequivalence studies, which define bioequivalence as "the absence of a significant difference in the rate and extent to which the active moiety becomes available at the site of action when administered at the same molar dose under similar conditions (11).

In order to test the primary hypothesis, log-transformed $AUC_{0-\infty}$ and C_{max} after a single dose for crushed/dissolved

Table 4

Confidence Level	Sample Size (N)	Target Distance from Mean to Limits	Actual Distance from Mean to Limits	Standard Deviation (S)
0.900	5	0.050	0.048	0.050
0.900	13	0.050	0.049	0.100
0.900	27	0.050	0.049	0.150
0.900	46	0.050	0.050	0.200
0.900	70	0.050	0.050	0.250
0.900	3	0.100	0.084	0.050
0.900	5	0.100	0.095	0.100
0.900	9	0.100	0.093	0.150
0.900	13	0.100	0.099	0.200
0.900	19	0.100	0.099	0.250
0.900	3	0.150	0.084	0.050
0.900	4	0.150	0.118	0.100
0.900	5	0.150	0.143	0.150
0.900	7	0.150	0.147	0.200
0.900	10	0.150	0.145	0.250
0.900	3	0.200	0.084	0.050
0.900	3	0.200	0.169	0.100
0.900	4	0.200	0.177	0.150
0.900	5	0.200	0.191	0.200
0.900	7	0.200	0.184	0.250
0.900	2	0.250	0.223	0.050
0.900	3	0.250	0.169	0.100
0.900	4	0.250	0.177	0.150
0.900	4	0.250	0.235	0.200
0.900	5	0.250	0.238	0.250

versus whole tablets will be compared. The adjusted mean differences will be estimated and their 90% confidence intervals calculated. In the case of $AUC_{0-\infty}$ and C_{max}, the estimated differences and confidence limits will be exponentiated in order to compare ratios between tablet forms.

Statistical Methods

The sample size was calculated according to the formulas for a multiplicative model (12). **Table 4** includes sample size calculations for this proposed study (13). If the mean C_{max} ratio or AUC ratio is 1, a sample size of 5 subjects produces a two-sided 90% confidence interval (0.952, 1.048) (i.e., a distance from the mean to the limits that is equal to 0.048, when the estimated standard deviation is 0.050). A sample size of 10 subjects produces a two-sided 90% confidence interval (0.855, 1.145) if the mean C_{max} ratio or AUC ratio is 1, and the estimated standard deviation is 0.25. Assuming a dropout rate of 10%, a sample size of 12 subjects will be required to provide 90% power to demonstrate the bioequivalence of C_{max} with 90% confidence intervals (CI) of 80% and 125%.

13.1 Data Management

The investigator will maintain and securely store complete, accurate, and current study records throughout the study. Pharmacokinetic data will be entered into Excel files and imported into WinNonlin for analysis. Non-compartmental PK will be performed for all ARVs. C_{max} and AUC will be compared across study arms consistent with FDA bioequivalence guidance. Laboratory data will be received electronically from the clinical laboratory. Laboratory data will be reviewed in printed format for clinically significant lab abnormalities with the paper copy serving as the source document. Clinical data will be collected on paper source documents with data being entered into a web-based password-secure database with an audit trail (e.g. REDCap). Data for ineligible subjects will be retained for purposes of improving recruitment strategies and to help understand why potential participants are not eligible to participate.

13.2 Accrual

The team expects to accrue 2-3 subjects per month. Expected time to reach full accrual of 12 evaluable participants, is 6-9 months.

14 HUMAN SUBJECTS

Education in the protection of human research participants has been met by certified completion of the Johns Hopkins University School of Medicine Web-based Research Compliance course, Human Subjects Research Training, by the study staff.

14.1 IRB and Informed Consent

The protocol and informed consent document and any subsequent modifications will be reviewed and approved by the JHU IRB. Written informed consent will be obtained by the study coordinators at the DDU unit during the screening visit. The purpose of the study, the procedures to be followed, risks, and benefits of participation will be explained. Subjects will be given as much time as they need to read, ask questions, and receive satisfactory answers about the consent form. A subject must

understand and give written consent to participate in the study. Comprehension of the consent form will be assessed by querying the patient about the study. A copy of the signed informed consent will be given to the participant, and the original retained by the investigator as part of the study.

14.2 Subject Confidentiality

All research materials will be obtained by the investigators strictly for research purposes. Each subject will be assigned a confidential study number. Data will be stored in a database on IBM PC compatible computers using only the confidential study number, without reference to participant's name. Access to subject study identification codes will be restricted to the principal investigator and study staff and upon request, to the JHU IRB or other regulatory agencies in compliance with HIPAA regulations. Data collected from the study containing PHI, will be stored on a secure password protected network accessible only to the study staff.

14.3 Definition of Adverse Events

The safety of all participants enrolled in this study will be monitored throughout the study. Safety monitoring will include history and physical examination, with vital signs, adverse event reporting, and laboratory evaluations. In addition, participants will be instructed to notify the study staff of any problems that occur between visits and, if necessary, will be evaluated by the investigator or study staff at an unscheduled interim visit.

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For the purposes of this protocol, all adverse events will be collected from the time of informed consent, but only those occurring following exposure to a dose of Genvoya will be analyzed.

Other adverse event Definitions: The following definitions of terms guided by the International Conference on Harmonization and the US Code of Federal Regulations apply to this section:

- Unexpected Adverse Event: An event in which the specificity or severity is not consistent with the current investigator's brochure, consent form, or other risk information. "Unexpected", as used in this definition, refers to an adverse drug experience that has not been previously observed.

- Related Adverse Event: Any event for which there is a reasonable possibility that the adverse experience may have been caused by the study drug but there is insufficient information to determine the likelihood of this possibility.

- Serious Adverse Event: Includes death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant

disability/incapacity, or any medical event that requires treatment to prevent one of the medical outcomes listed above.

- Life-threatening, for the purpose of reporting adverse events, refers to an event in which the patient was, in the view of the initial reporter, at immediate risk of death at the time of the event as it occurred (i.e., it does not include an event that, had it occurred in a more serious form, might have caused death).

14.4 Reporting of Adverse Events

All events will be reported to the JHU IRB and to other regulatory agencies as needed. Serious adverse other than death and immediately lifer threatening events will be reported within 10 business days after sponsor initial receipt of the information. Death and immediately lifer threatening events will be reported within 3 business days Non serious adverse events will be reported to the JHU IRB in the annual review report.

14.5 Steps to Minimize the Risks

Subjects will be evaluated as indicated in the schedule of events, or more frequently if medically indicated. If clinically indicated, directed physical examination, vital signs andsafety laboratory tests will be performed during outpatient visits. Additional laboratory tests may be undertaken for a participant, if medically indicated. Subjects experiencing toxicity will be followed until resolution, return to baseline values, stabilization, or an adequate explanation can be given for their condition.

Genvoya is a FDA approved medication for the treatment of HIV infection. This fixed combination of ARV drugs is known to be well tolerated. This is a short duration study with only two doses of Genvoya. Side effects observed with Genvoya are usually associated with long term administration of this ARV medication. Participants in this study will be healthy research participants that will be given only two doses of Genvoya. Therefore, the short duration of this study and short medication exposure in health research participants makes it less likely that participants will experience clinically important adverse events.

14.6 Potential Benefits of the Proposed Research

There are no benefits for the participants enrolled in this study.

14.7 Importance of the Knowledge to be Gained

This study will determine whether crushed/dissolved Genvoya tablet is bioequivalent to the whole tablet formulation. Confirming bioequivalence between these two tablet forms will provide HIV-infected subjects with the option of using the crushed/dissolved Genvoya tablet if they have difficulty swallowing the whole tablet formulation.

14.8 Inclusion of Women, Minorities, and Children

This bioequivalence study will focus on adult men and women healthy research participants. All efforts will be made to enroll minorities in this study.

14.9 Compensation

This study will be conducted at no cost to the participant. Participants will be compensated up to $900 to complete the study and parking validation will be provided for the long Day 1 PK study visits, if applicable. There are no financial penalties for not completing the study. All costs for the study will be covered for by the study.

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APPENDIX

Table S1. Estimated fractional change of sequential samples relative to T_{max} during rise before and decay after C_{max}.

Drugs	PK Parameters		Sampling Hour														Samples relative to T_{max}		
	Half-life	Tmax	0.25	0.5	0.75	1	1.5	2	3	4	5	6	10	14	24	48	72	Before	After	Half-lives After
EVG	12.9	4				0.25		0.50	0.75	T_{max}	0.06	0.06	0.24	0.24	0.71	2.63	2.63	3	7	5.6
COBI	3.5	3		0.17		0.25		0.67	T_{max}	0.22		0.49	1.21	1.21	6.25	114.93	.	3	6	13.7
FTC	10	3		0.17		0.25		0.67	T_{max}	0.07		0.15	0.32	0.32	1.00	4.28	4.28	3	7	7.2
TAF	0.51	1	0.25	0.50	0.75	T_{max}	0.97	0.97	2.89	2.89	2.89	14.15	.	.	.	.	.	3	6	11.8
TFV	32	1.5	0.17	0.33	0.50	0.67	T_{max}	0.01	0.02	0.02		0.04	0.09	.	0.35	0.68	0.68	4	8	2.3