Efficacy, Safety, and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Adults with HIV-HBV Coinfection

(BEST-HBV)

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PROTOCOL SYNOPSIS

Title: Efficacy, Safety, and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Adults with HIV-HBV Coinfection.

Short Title: BEST-HBV

Disease: Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) coinfection.

Primary Objective:

- To evaluate the efficacy of fixed dosed combination (FDC) bictegravir/emtricitabine/ tenofovir alafenamide (B/F/TAF) in adult subjects coinfected with HIV-1 and HBV, as determined by HIV-1 RNA <50 copies/mL at Week 24 by US FDA Snapshot Algorithm and/or HBV DNA <29 IU/mL at Week 24 by missing = failure method.

Secondary Objectives:

- Evaluate the safety and tolerability of FDC B/F/TAF in HIV-HBV coinfected subjects.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot Algorithm.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by HBV DNA <29 IU/mL at Week 48 by missing = failure method.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by improvement in CD4 count, ALT normalization, HBeAg loss, HBsAg loss, and improvement in FibroScan test scores from baseline to Week 24 and Week 48.

Primary Endpoints:

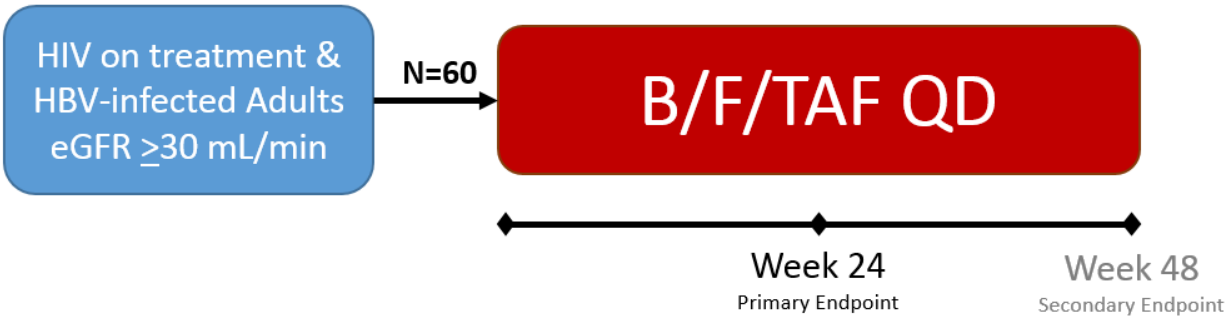
- Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 by FDA Snapshot Algorithm.
- Proportion of subjects with HBV DNA <29 IU/mL at Week 24 by missing = failure method.

Secondary Endpoints:

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot Algorithm.
- Proportion of subjects with HBV DNA <29 IU/mL at Week 48 by missing = failure method.
- Assessment of the safety and tolerability of the FDC B/F/TAF in HIV-HBV coinfected subjects as measured by the proportion of subjects who discontinue study medications due to AE.
- Change from baseline in CD4 cell count and percentage at Week 24 and at 48.
- Proportion of subjects with normalized ALT at Week 24 and Week 48.
- Proportion of subjects with HBV e antigen (HBeAg) loss and seroconversion to anti-HBe at Week 24 and Week 48.

- Proportion of subjects with HBV surface antigen (HBsAg) loss and seroconversion to anti-HBs at Week 24 and Week 48.
- Change from baseline in Fibroscan test score at Week 24 and Week 48.

Study Design:
This is a multicenter, open-label phase 4 study to evaluate the efficacy, safety, and tolerability of treatment with fixed dosed combination bictegravir/emtricitabine/tenofovir alafenamide in adults with HIV-1 and HBV coinfection who are currently on a stable antiretroviral regimen for at least 3 months. Subjects who provide written informed consent and meet all eligibility criteria will receive FDC Bictegravir 50 mg/Emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food. Enrolled subjects will be followed up for 48 weeks.



Target Population: Adults with HIV/HBV coinfection currently on stable antiretroviral regimen for at least 3 months.
Phase of Development: Phase 4.
Duration of Treatment: 48 weeks.
Estimated sample size: 60 participants.
Estimated number needed to screen to achieve sample size: 75.
Estimated Accrual Period: 12 months.

Inclusion Criteria:
- Age 18 years or older at enrollment.
- Documented HIV-1 infection and currently on a stable regimen for at least 3 months prior to enrollment.
- No known history of resistance to tenofovir alafenamide (TAF), emtricitabine (FTC), or Bictegravir (BIC) except M184V and M184I. Those with M184V or M184I mutations will be allowed to enroll in the study.
- Documented chronic HBV infection, based on any of the following:

a. Positive HBsAg result or nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) or positive HBeAg on two occasions at least 6 months apart (any combination of these tests performed 6 months apart is acceptable); or
b. Negative immunoglobulin M (IgM) antibodies to HBV core antigen (anti-HBc IgM) AND a positive results on one of the following tests: HBsAg, HBeAg, or nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) prior to or at screening.

- No current or prior regimen containing three active anti-HBV agents (drugs active against HBV includes lamivudine [3TC], adefovir [ADV], entecavir [ETV], emtricitabine [FTC], tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide [TAF]).
- Must have a primary care provider(s) for medical management.
- Females of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix F) from screening and throughout the duration of the study. Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study drug dosing.
- Male subjects must be willing to abstain from heterosexual intercourse or use a condom throughout the study period.
- Stated willingness to comply with all study procedures and availability for the duration of the study.
- Written informed consent must be obtained before any study procedure is performed.

Exclusion Criteria:

- Women who are pregnant or breastfeeding.
- Any known allergies to any of the components of B/F/TAF.
- Treatment with another investigational drug within three months of enrollment.
- Abnormal hematological and biochemical parameters at screening, including:
    a. Absolute neutrophil count (ANC) < 750 cells/mm^3.
    b. Platelets < 50,000/mm^3.
    c. Hemoglobin < 8.5 g/dL.
    d. AST or ALT of > 5 times upper limit of normal (ULN).
    e. Estimated GFR < 30 mL/min/1.73 m^2.
    f. Total bilirubin > 1.5 times ULN.
- Previous or current history of malignancy, other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma. Note: Those with a history of malignancy who are in remission for two or more years may be included in the study.

- An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening.
- Subjects experiencing decompensated cirrhosis (e.g. ascites, encephalopathy, or variceal bleeding).
- Acute hepatitis in the 30 days prior to study entry.
- Active tuberculosis infection.
- Subjects receiving ongoing therapy with any medications contraindicated for co-administration with B/F/TAF FDC, including but not limited to the following medications in the table below:

Drug Class	**Prohibited Agents[#]**
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbamazepine
Antimycobacterials	Rifampin, Rifapentine, rifabutin
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea
Miscellaneous agents	Mitotane

[#] Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

- Current alcohol or substance use that in the opinion of the investigator may interfere with subject study compliance
- Any other clinical conditions that in the opinion of the investigator would make the subject unsuitable for the study or unable to comply with the dosing requirements

Sample Size Justification & Statistical Analysis:

The primary analysis endpoint to evaluate treatment efficacy used to compute the sample size is the observed HIV-1 viral suppression rate. A true suppression rate at Week 24 of at least 91% would be considered active in this patient population. An exact binomial test with a 0.05 type I error rate will have 84% power to detect the difference between the null hypothesis proportion (number of suppressed/total number treated) of 0.773 (based on published results) and the research hypothesis proportion of 0.910 (our educated guess on the desired rate of success) when the sample size is 60.

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LIST OF ABBREVIATIONS

ABBREVIATIONS	DEFINITIONS
3TC	Lamivudine
ABC	Abacavir
ADV	Adefovir
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HBc (or HBcAb)	Hepatitis B core antibody
Anti-HBe (or HBeAb)	Hepatitis B e antibody
Anti-HBs (or HBsAb)	Hepatitis B surface antibody
APR	Antiretroviral Pregnancy Registry
AST	Aspartate aminotransferase
AUC	Area under the curve
B/F/TAF	Bictegravir/emtricitabine/tenofovir alafenamide
BP	Blood pressure
BIC	Bictegravir
BRCP	Breast cancer resistance protein
c	Cobicistat (e.g., as component of EVG/c/FTC/TAF)
CBC	Complete blood count
CFR	Clinical Research Unit
CI	Confidence Interval
C_{max}	Maximum concentration of a drug achieved after dosing
CMP	Comprehensive metabolic panel
CRU	Clinical Research Unit
CYP	Cytochrome P450 enzyme
DAIDS	Division of Acquired Immune Deficiency Syndrome
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DOH	Department of Health
DTG	Dolutegravir
ECG	Electrocardiogram
EVG	Elvitegravir
FDA	(US) Food and Drug Administration
FDC	Fixed dose combination
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBcrAg	Hepatitis B core related antigen

HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polyethylene
HDV	Hepatitis D virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hsCRP	High sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgM	Immunoglobulin M
IHV	Institute of Human Virology
INR	International normalized ratio
INSTI	Integrase stand transfer inhibitor
IRB	Institutional Review Board
IU	International units
MATE	Multidrug and toxin extrusion transporter
mL	Milliliter
N	Number
NCT	National Clinical Trial
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
OCT	Organic cation transporter
OHRP	Office for Human Research Protection
P	Pulse rate
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
P-gp	P-glycoprotein
PI	Principal Investigator
PT	Prothrombin time
PTT	Partial thromboplastin time
PVE	(Gilead Sciences) Pharmacovigilance and Epidemiology
QA	Quality assurance
QC	Quality control
QD	Once daily (i.e. *quaque die*)
R	Respiratory rate
RAL	Raltegravir
RAV	Resistance associated variant
RBC	Red blood cell (erythrocyte) count

RHD	Recommended human dose
RNA	Ribonucleic acid
SAE	Serious adverse event
SAR	Suspected adverse reaction
SC	Study coordinator
SMC	Safety Monitoring Committee
T	Temperature
$t_{1/2}$	Half-life
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
U.S.	United States
VL	Viral load
WBC	White blood cell count
WOCP	Woman of childbearing potential
Wt	Weight

1 INTRODUCTION

1.1 Background & Scientific Rationale

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of global public health importance. More than 37 million people worldwide are living with HIV-1 infection. Of these HIV-1 infected populations, about 5-20% are also coinfected with the hepatitis B virus (HBV) (Singh K, et al. 2017). In the United States (U.S.), about 10% of people with HIV are coinfected with HBV, and about 20% of all new HBV infections are among gay and bisexual men (CDC Fact Sheet 2017). HIV-HBV coinfection has been associated with a higher risk of morbidity and mortality, especially with regard to accelerated liver disease progression leading to hepatic failure, need for liver transplantation, and death (Colin JF, et al. 1999; Thio CL 2002). In addition, HBV coinfection accelerates immunologic and clinical progression of HIV infection as well as increases the risk of hepatotoxicity when combination antiretroviral therapy (ART) are used (Sun HY et al. 2014). Nevertheless, the availability of HBV-active ART regimens has significantly improved the outcome of the HIV-HBV coinfected population, leading to longer life expectancies and lower rates of morbidities.

The University of Maryland Medical System has multiple clinical practices that care for patients living with HIV-1 and chronic HBV. Close to four thousand patients infected with HIV-1 are under its care. The estimated prevalence rate of HIV-HBV coinfection in these clinical practices are between 2-3%. The HIV/HBV target population is predominantly Black or of African American heritage (89%) followed by White (9.6%), and close to 80% are males. Approximately 87% are already on tenofovir (either TDF or TAF) based regimen as part of their backbone NRTI. In addition, majority of these coinfected patients are on integrase inhibitor (63.8%), though some are still on NNRTIs (14.5%) and others on various protease inhibitors (21.7%). Of those on integrase inhibitors, two-thirds are on dolutegravir (65.9%), while the rest are on either elvitegravir (27.3%) or raltegravir (6.8%).

1.1.1 Tenofovir alafenamide in HIV-HBV Coinfection

Tenofovir, in the form of tenofovir disoproxil fumarate (TDF) has been one of the mainstay agents for the treatment of chronic HBV infection. Tenofovir disoproxil fumarate has demonstrated potency and predictable high long-term efficacy resulting in sustained HBV viral suppression with favorable safety profile (EASL 2017). The durability of tenofovir based therapy has been well documented with published data as long as 7-years showing 99.3% of patients (N=427) taking TDF maintaining viral suppression. In this publication by Dr. Maria Buti and colleagues, 80% had ALT normalization, and close to 12% of HBeAg-positive chronic HBV subjects had HBsAg loss (Buti M et al. 2015). Long-term therapy with TDF was also associated

with regression of fibrosis in up to 80% by year 5 (Marcellin P et al. 2013). In addition, no resistance to TDF was detected in these multi-year studies (Buti M et al. 2015). The lack of resistance-associated variants (RAV) developing during TDF therapy has be thought to be related to several possible factors including: (1) the high binding affinity of tenofovir to YMDD (the HBV reverse transcriptase target); (2) higher (30 times) dosage of the tenofovir (compared to other anti-HBV drugs such as adefovir); and (3) the constrained mutational space due to gene overlap in HBV genome (Van Hemert et al. 2014).

Tenofovir alafenamide (TAF) is a phosphonated prodrug of tenofovir, developed by Gilead Sciences, due to its enhanced plasma stability compared to TDF. This allows higher levels of the active intracellular form of tenofovir diphosphate to concentrate in target cells such as the hepatocytes and lymphoid cells, for the treatment of HBV and HIV-1, respectively (Mukurami E et al 2013; Birkus G et al. 2012). As it is able to remain mostly intact in the plasma, TAF administration is associated with reduced systemic tenofovir exposure compared to TDF, resulting in corresponding reduction in renal or bone complications (Agarwal K et al. 2015).

The efficacy of TAF against chronic HBV infection has been demonstrated in 2 phase III clinical trials. Among HBe antigen negative chronic HBV patients, TAF was found to be non-inferior to TDF at 48 weeks with HBV DNA suppression (defined as <29 IU/mL) of 94% vs 93%, respectively (Buti M, et al. 2016). Similarly, among patients with positive HBeAg at baseline, TAF was also found to be non-inferior to TDF with HBV suppression rates of 64% versus 67% (p-value not significant), respectively (Chan HLY, et al. 2016). In these studies, TAF had a more favorable side effect profile with fewer declines in bone marrow density and smaller changes in renal safety parameters compared to TDF at 48 weeks. Tenofovir alafenamide has been used as a component of elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide (EVG/c/FTC/TAF) for adults with HIV-HBV coinfection in an open-label noncomparative switch study in Study 1249. In this study, at 48 weeks of EVG/c/FTC/TAF, 91.7% of the 72 subjects maintained or achieved virologic suppression (HIV-1 RNA <50 copies/mL and HBV DNA <29 IU/mL) (Gallant J et al. 2016). The seroconversion rate was 2.9% in HBsAg-positive subjects and in 3.9% of HBeAg-positive subjects. Those with abnormal ALT at baseline, 40% had ALT normalization. TAF is a major component of the FDC B/F/TAF that is to be investigated in this study.

1.1.2 Bictegravir: New HIV-1 Integrase Strand Transfer Inhibitor

Bictegravir (BIC) is a recently approved integrase strand transfer inhibitor (INSTI) with a longer dissociation half-life from wild-type and G140S+Q148H mutant integrase-DNA complexes in vitro than other INSTIs, including dolutegravir (DTG), raltegravir (RAL), and elvitegravir (EVG) (White K, et al. 2017). Therefore, BIC is predicted to have a higher genetic barrier to resistance than other integrase inhibitors. Bictegravir has a more potent antiviral activity against

G140S/Q148H integrase variants in vitro than DTG (Hightower K, et al. 2011). In addition, BIC has a better resistance profile compared to DTG, based upon in vitro data from patient-derived clinical isolates (While K, et al. 2016; Tsiang M, et al. 2016). Bictegravir does not require boosting (unlike EVG) and therefore has less drug-drug interaction potential. Bictegravir is currently available only in a fixed-dose combination (FDC) tablet, coformulated with Emtricitabine (FTC) and tenofovir alafenamide (TAF), administered as a one pill, once daily regimen, and is given with or without food.

1.2 Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF)

1.2.1 Description

Bictegravir/emtricitabine/tenofovir alafenamide is FDA-approved (approval date February 2018) fixed dose combination drug regimen under the brand name BIKTARVY® (Gilead Sciences Inc.). It is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (i.e. HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen (Biktarvy 2018). Bictegravir/emtricitabine/tenofovir alafenamide contains an HIV-1 integrase strand transfer inhibitor, bictegravir, and two HIV-1 nucleos(t)ide analog reverse transcriptase inhibitors, tenofovir alafenamide (TAF) and emtricitabine (FTC). Both TAF and FTC have activity against HBV infection. B/F/TAF is a complete regimen that has the potential to offer HIV-HBV coinfected patients a simple, once daily regimen containing drug components that provides a high barrier to resistance against both HIV-1 and HBV. B/F/TAF does not require boosting, and potentially offers an effective and safe alternative to other regimens, without need for human leukocyte antigen (HLA) testing or close monitoring of renal or bone toxicities.

1.2.2 Nonclinical Toxicology and Pharmacology

1.2.2.1 Studies of Carcinogenesis, Mutagenesis, and Impairment of Fertility

Bictegravir was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 100 mg/kg/day in males and 300 mg/kg/day in females. BIC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays. BIC did not affect fertility, reproductive performance or embryonic viability in male and female rats at 29 times higher exposures (area under the curve [AUC]) than in humans at the recommended dose of 50 mg BIC in B/F/TAF (BIKTARVY®). (Biktarvy 2018)

Emtricitabine, in long-term carcinogenicity studies, was found to have no drug-related increases in tumor incidence found in mice at doses up to 750 mg per kg per day (25 times the human systemic exposure at the recommended dose of 200 mg per day in B/F/TAF), or in rats at doses up to 600 mg per kg per day (30 times the human systemic exposure at the recommended dose

in B/F/TAF). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays. Emtricitabine did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dose in BIKTARVY. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dose in B/F/TAF (BIKTARVY®). (Biktarvy 2018)

Since tenofovir alafenamide (TAF) is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and four times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 151 times (mice) and 51 times (rat) those observed in humans after administration of the daily recommended dose of B/F/TAF (BIKTARVY®). At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 151 times (BIKTARVY®) the exposure observed in humans. In rats, the study was negative for carcinogenic findings. Tenofovir alafenamide was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays. There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation. (Biktarvy 2018)

1.2.2.2 Animal Toxicology and Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three-month recovery period. No eye toxicity was observed in the dog at systemic exposures of seven (TAF) and 14 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in B/F/TAF (BIKTARVY®). (Biktarvy 2018)

1.2.3 Clinical Pharmacology

1.2.3.1 Mechanism of Action

Bictegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), and HIV-1 encoded enzyme that is required for viral replication. Inhibition of

integrase prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus. (Biktarvy 2018)

Emtricitabine is a synthetic nucleoside analog of cytidine, and is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, Ɛ, and mitochondrial DNA polymerase γ. (Biktarvy 2018)

Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture. (Biktarvy 2018)

Tenofovir alafenamide has clinical trial proven activity against HBV. Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is then converted to tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated by cellular kinase to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerase that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture. (Vemlidy 2018)

1.2.3.2 Pharmacodynamics

Cardiac electrophysiology studies were conducted in a QT/QTc trial that enrolled 48 health volunteers. In this study, BIC at doses 1.5 to 6 time recommended dose did not affect the QT/QTc interval and did not prolong the PR interval. TAF at the recommended dose or at a dose 5 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval. The effect of FTC on the QT interval is not known. (Biktarvy 2018)

In studies with healthy subjects, the mean change from baseline in serum creatinine with administration of BIC 75 mg (1.5 times the approved recommended dosage) once daily with food for 14 days was 0.1 mg per dL on Days 7 and 14 compared to placebo. BID did not have significant effect on the estimated creatinine clearance or on the actual glomerular filtration rate. (Biktarvy 2018)

1.2.3.3 Pharmacokinetics

The pharmacokinetic (PK) properties of B/F/TAF components are summarized in **Table 1-1**. The multiple dose PK parameters of BIC, FTC, and TAF based on population pharmacokinetic analysis as well as a more complete PK description of the regimen and its components are found in the BIKTARVY U.S. package insert published by Gilead Sciences Inc. It should be noted that the pharmacokinetics of B/F/ TAF have not been evaluated in subjects coinfected with HBV.

Table 1-1: Pharmacokinetic Properties of BIC, FTC, and TAF

	BIC	FTC	TAF
Absorption			
t_{max} (hours)	2.0 - 4.0	1.5 - 2.0	0.5 - 2.0
Effect of high fat mean (relative to fasting)			
AUC ratio	1.24 (1.16, 1.33)	0.96 (0.93, 0.99)	1.63 (1.43, 1.85)
C_{max} ratio	1.13 (1.06, 1.20)	0.86 (0.78, 0.93)	0.92 (0.73, 1.14)
Distribution			
% bound to human plasma protein	>99%	<4%	~80%
Blood-to-plasma ratio	0.64	0.6	1.0
Elimination			
$t_{1/2}$ (hours)	17.3 (14.8, 20.7)	10.4 (9.0	0.51 (0.45, 0.62)
Metabolism			
Metabolic pathway(s)	CYP3A UGT1A1	Not significantly metabolized	Cathepsin A (PBMC) CES1 (hepatocytes)
Excretion			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine	35%	70%	<1%
% of dose excreted in feces	60.3%	13.7%	31.7%

The half-life of tenofovir diphosphate, the active metabolite of TAF, is between 150-180 hours within the hepatocytes. In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages, and by carboxylesterase 1 (CES1) in hepatocytes.

1.2.4 Clinical Studies on Bictegravir/Emtricitabine/Tenofovir Alafenamide

Bictegravir/Emtricitabine/tenofovir alafenamide (B/F/TAF) has been clinically shown to be highly effective in the treatment of HIV-1 infection based upon two phase 3 treatment-naïve trials, the Study 1489 and Study 1490. In Study 1489 study (Gallant J, et al. 2017), N = 631, B/F/TAF demonstrated non-inferiority to DTG/ABC/3TC (VL ≤ 50 copies/mL at 48 weeks, B/F/TAF 92.4% vs. DTG/ABC/3TC 93.0%, p=0.78). No treatment emergent resistance developed in either treatment arm. This study excluded HIV-HBV coinfected patients. In Study 1490 (Sax PE, et al. 2017), N = 742, B/F/TAF demonstrated non-inferiority to DTG + TAF/FTC (VL ≤ 50 copies/mL at 48 weeks, BIC 89% vs DTG 93%, p=0.12). There were no treatment emergent resistance in either arm. In contrast to the previous study, HBV coinfection were allowed to be enrolled in Study 1490. Nevertheless, of the 320 patients in the study who received B/F/TAF, only eight (2%) subjects were coinfected with HBV (Sax PE, et al. 2017).

1.3 B/F/TAF in HIV-HBV Coinfection & Study Hypothesis

Though the safety and efficacy of B/F/TAF has been well established in the treatment of HIV-1 infection and TAF has been found to be as efficacious and durable as TDF in the treatment of HBV infection, there is limited data on the use of B/F/TAF in the HIV-HBV coinfected subpopulation. The 2 phase III registration studies (Treatment-naïve Study 1490 and switch Study 1878) that allowed HIV/HBV coinfected subjects to be enrolled had a total of only 16 coinfected subjects who received B/F/TAF (Gallant J, et al. 2017, Sax PE, et al. 2017). In Study 1490, all eight coinfected participants who received B/F/TAF had HIV-1 RNA ≤50 copies/mL and HBV DNA <29 IU/mL at Week 48 (Rockstroh JK et al. 2018). Likewise, in Study 1878, all eight volunteers with HIV-HBV coinfection maintained suppression against both viruses (Rockstroh JK et al. 2018). Thus, there is a need for additional data to further validate the use of B/F/TAF as a mainstay regimen in the treatment of HIV-HBV coinfected people. This study will be conducted to obtain real-world data in a larger population to help address this need. The main hypothesis of this study is that fixed-dose combination (FDC) B/F/TAF is safe and efficacious in the treatment of adults coinfected with HIV-1 and HBV virus.

1.4 Risk and Benefit Assessments

1.4.1 Risk of using B/F/TAF (BIKTARVY®)

1.4.1.1 Adverse Events in Clinical Trials

The most common adverse events reported in at least 5% of subjects in those who have taken B/F/TAF are diarrhea, nausea, and headache. The proportion of subjects who discontinued treatment with B/F/TAF due to adverse events, regardless of severity was 1%. The majority (87%) of adverse events associated with B/F/TAF were Grade 1. **Table 1-2** displays the

frequency of adverse events greater than or equal to 2% in the two treatment naïve registry studies (Study 1489 and study 1490), attributed to study drug by the investigator. (Biktarvy 2018)

Table 1-2: Adverse Reactions (All Grades) Reported in >2% of HIV Infected Adults with No Antiretroviral Treatment History Receiving B/F/TAF in Study 1489 or 1490 (Week 48 Analysis)

Adverse Reactions	Study 1489 N=314	Study 1490 N=325
Diarrhea	6%	3%
Nausea	5%	3%
Headache	5%	4%
Fatigue	3%	2%
Abnormal dreams	3%	<1%
Dizziness	2%	2%
Insomnia	2%	2%

1.4.1.2 Pregnancy and Breastfeeding Risks

The prevalence of birth defects per 100 live births among HIV-1 infected women with a first trimester exposure to any ART is 2.7 (95% confidence interval (CI): 2.4-3.1), i.e. 255 outcomes with defects of 9,336 live births according to the Antiretroviral Pregnancy Registry, January 2018 interim report (AP Registry 2018). This prevalence of defects was not significantly different from those with an initial exposure during the 2nd and 3rd trimester, nor was it different from non-HIV population based pregnancy registries (AP Registry 2018). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

A pregnancy exposure registry (The Antiretroviral Pregnancy Registry or APR) is being used to monitors pregnancy outcomes in women exposed to B/F/TAF during pregnancy. Currently, there is insufficient human data on the use of B/F/TAF during pregnancy to inform of drug-associated risk of birth defects and miscarriage. Both BIC and TAF use in pregnant women have not been evaluated. There is a limited number of women with use of FTC use during pregnancy reported in the APR with prevalence rates not different from general population (AP Registry 2018). (Biktarvy 2018)

In animal studies, there is no evidence of adverse reproductive developmental outcomes observed with any of the components of B/F/TAF at exposure that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended human

dose (RHD). During organogenesis, systemic exposures to BIC were approximately 36 (rats) and 0.6 times (rabbits), to FTC were approximately 60 (mice) and 108 times (rabbits), and to TAF were approximately two (rats) and 78 times (rabbits) the exposure at the recommended human dose of B/F/TAF. (Biktarvy 2018)

The Center for Disease Control and Prevention recommends that HIV-1 infected mothers in the U.S. not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Nevertheless, it is not known whether B/F/TAF or any of its components are present in human breast milk, affects human milk production, or has effects on the breastfeeding infant. (Biktarvy 2018)

As the effects of B/F/TAF on an unborn baby or a nursing infant are not known, care must be taken to avoid pregnancy in female subjects or in female partners of male subjects during this study and following completion of study treatment (30 days after completion for women, 14 days after completion for men). Subjects will be excluded if they are pregnant, planning to become pregnant, or while breast-feeding.

1.4.2 Risk of FibroScan® Test

FibroScan® is a noninvasive diagnostic ultrasound based device used to measure liver scarring, or fibrosis, caused by various diseases including HBV. It provides a non-surgical alternative to liver biopsy to assess liver damage.

In preparation for this procedure, subjects will be advised not to eat or drink (excluding water) for at least 3 hours prior to procedure. The FibroScan® test usually takes about 5-10 minutes. During the procedure, the subject will lie supine on his/her back with the right arm raised behind his/her head and the right abdominal area is exposed. A trained study staff member will apply a water-based gel to the skin and place the non-invasive probe over the liver area.

Fasting prior to procedure can result in hypoglycemia, lightheadedness or fainting. During the procedure, there is a small but possible risk of localized allergic reaction and irritation related to the water-based lubricating gel as well as discomfort due to positioning while in supine position.

1.4.3 Risk of Blood Draw

Collecting blood samples from a vein may cause pain, bruising, lightheadedness, fainting, bleeding and rarely infection at the site of the needle stick.

1.4.4 Risk of Electrocardiogram (ECG)

After an ECG, subjects may experience mild skin irritation, slight redness or itching where the recording patches were placed. They may also need to have chest hair shaved for the procedure.

1.4.5 Risk of Allergic Reactions

Allergic reaction is always possible with a drug that the study participant has never been exposed to before. Serious allergic reactions that can be life-threatening may occur. Some things that happen during any allergic reaction to any type of medication are: rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat, or eyes, fast pulse, and/or sweating may occur. Study participants will be monitored closely for any reactions.

1.4.6 Risk of Loss of Confidentiality

There is always a potential for the loss of confidentiality. This risk will be minimized by keeping all study data stored and secured. Electronic data will be password protected. Private information will only be given out as listed in the Health Insurance Portability and Accountability Act (HIPAA) form.

1.4.7 Unexpected Risk and Discomforts

There may be risks in this study that are not yet known, or that happens rarely when subjects take these study drugs. Subjects will be told of any new information that could affect their safety during study participation.

1.4.8 Potential Benefits

All patients with HIV-1 infection should receive effective antiretroviral therapy. Selection of drugs for HIV-1 patients coinfected with HBV should take into consideration the regimen's anti-HBV activity to prevent potentially life-threatening hepatitis flares. B/F/TAF FDC regimen has the potential to offer HIV-HBV infected patients a simple, once daily regimen containing drug components that provides a high barrier to resistance against both HIV-1 and HBV. B/F/TAF does not require a boosting agent, and offers an effective and safe alternative to other regimens, without need for HLA testing or close monitoring of renal or bone toxicities. In addition, patient participation in this study will contribute to the body of knowledge about treatment for HIV-HBV coinfection.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of fixed dosed combination (FDC) bictegravir/emtricitabine/ tenofovir alafenamide (B/F/TAF) in adult subjects coinfected with HIV-1 and HBV, as determined by HIV-1 RNA <50 copies/mL at Week 24 by US FDA Snapshot Algorithm and/or HBV DNA <29 IU/mL at Week 24 by missing = failure method.

2.2 Secondary Objectives

- Evaluate the safety and tolerability of FDC B/F/TAF in HIV-HBV coinfected subjects.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot Algorithm.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by HBV DNA <29 IU/mL at Week 48 by missing = failure method.
- Evaluate the efficacy of FDC B/F/TAF in adult subjects coinfected with HIV-1 and HBV, as determined by improvement in CD4 count, ALT normalization, HBeAg loss, HBsAg loss, and improvement in Fibroscan test scores from baseline to Week 24 and Week 48.

2.3 Exploratory Objectives

- Evaluate changes in quantitative HBsAg levels during treatment with FDC B/F/TAF.
- Evaluate any changes in immune activation markers (plasma hsCRP, IL-6, TNF-α, and D-dimer and cellular HLA-DR+CD38+ CD4 and CD8 T lymphocytes) during treatment with FDC B/F/TAF.

2.4 Primary Endpoints

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 by FDA Snapshot Algorithm.
- Proportion of subjects with HBV DNA <29 IU/mL at Week 24 by missing = failure method.

2.5 Secondary Endpoints

- Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 by FDA Snapshot Algorithm.
- Proportion of subjects with HBV DNA <29 IU/mL at Week 48 by missing = failure method.
- Assessment of the safety and tolerability of the FDC B/F/TAF in HIV-HBV coinfected subjects as measured by the proportion of subjects who discontinue study medications due to AE.
- Change from baseline in CD4 cell count and percentage at Week 24 and at 48.

- Proportion of subjects with normalized ALT at Week 24 and Week 48.
- Proportion of subjects with HBV e antigen (HBeAg) loss and seroconversion to anti-HBe at Week 24 and Week 48.
- Proportion of subjects with HBV surface antigen (HBsAg) loss and seroconversion to anti-HBs at Week 24 and Week 48.
- Change from baseline in Fibroscan test score at Week 24 and Week 48.

2.6 Exploratory Endpoints

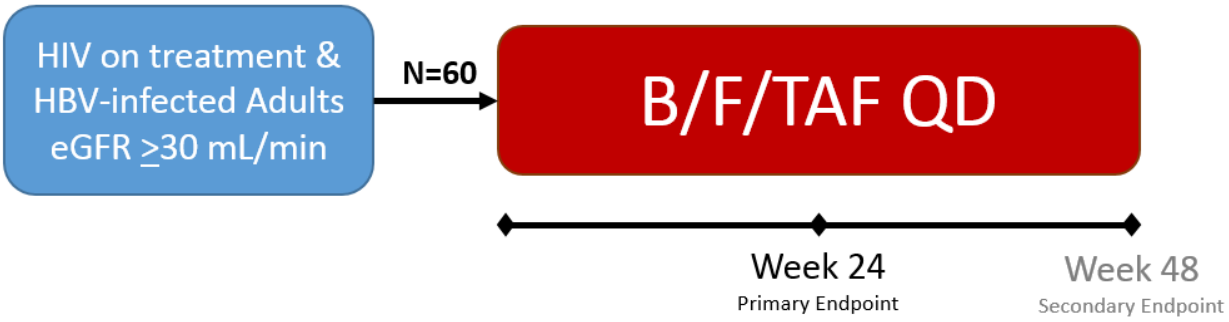
- Change from baseline in quantitative HBsAg at Week 24 and Week 48.
- Assessment of changes in immune activation markers (plasma hsCRP, IL-6, TNF-α, and D-dimer and cellular HLA-DR+CD38+ CD4 and CD8 T lymphocytes) during treatment with FDC B/F/TAF.

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a multicenter, open-label phase 4 study to evaluate the efficacy, safety, and tolerability of treatment with fixed dosed combination bictegravir/emtricitabine/tenofovir alafenamide in adults with HIV-1 and HBV coinfection who are currently on a stable antiretroviral regimen for at least 3 months. Two sites are planned to participate: Institute of Human Virology (IHV), University of Maryland, Baltimore, MD and Philadelphia Department of Health (DOH) Clinic. Subjects who provide written informed consent and meet all eligibility criteria will receive fixed dose combination of Bictegravir 50 mg/Emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF) administered orally one pill once daily, without regard to food. Study treatment duration for enrolled subjects will be 48 weeks. Safety evaluations will consist of adverse event, physical examination (including vital signs), and clinical laboratory data. Efficacy will be evaluated by HIV RNA and HBV DNA levels.

Figure 3-1. Study Schema



3.2 Study Procedures

See also Schedule of Activities (Appendix A).

3.2.1 Pretreatment Assessments

3.2.1.1 Screening Assessments (Day -90 to Day -3)

The following screening assessments must be done to determine subject eligibility. Written consent will be obtained before conducting any study procedures.

- Screen for inclusion/exclusion (see Section 5).
- Medical History.
- Complete physical examination, including weight, height, and vital signs (blood pressure, respiratory rate, heart rate, and temperature).
- Collect concomitant medication information.
- 12-lead electrocardiogram (ECG).
- Plasma HIV-1 RNA.
- Plasma HBV DNA.
- Quantitative HBsAg level.
- CD4 cell count.
- HBV profile [HBsAg, HBeAg, anti-HBs, anti-HBe, and anti-HBc both IgM and total].
- HCV serology.
- HDV serology.
- Complete blood count [hematocrit, hematocrit, erythrocyte count (RBC), white blood cell count (WBC), percentage and absolute WBC differential counts, platelet count].
- Comprehensive metabolic panel [glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, total carbon dioxide, calcium, total protein, albumin, total globulin, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase].
- Coagulation tests [activated partial thromboplastin time (PTT), prothrombin time (PT), international normalized ratio (INR)].
- Urinalysis.
- Serum pregnancy test for women of childbearing potential (defined as a woman who is physiologically capable of becoming pregnant).

With the exception of the serum pregnancy test, outside clinical laboratory tests may be used for screening if it was done within 90 days of screening.

3.2.2 Day 1 Assessments

Screening tests must be available before the subject is eligible for study participation. Once screening is completed and the subject meets all eligibility criteria, the subject will obtain baseline evaluations. Study drug administration may occur after completion of all baseline procedures.

Before Study Drug Administration:

- Review eligibility criteria (see Section 5) and confirm eligibility of subject.
- Obtain interval medical history.
- Conduct complete physical examination, including weight and vital signs [blood pressure (BP), respiratory rate (R), heart rate (HR), and temperature (T)].
- Collect concomitant medication information.
- Plasma HIV-1 RNA
- Plasma HBV DNA.
- Quantitative HBsAg level.
- CD4 cell count.
- HIV-1 genotype/phenotype, if HIV-1 RNA is ≥500 copies/mL.
- HBV genotype and resistance assay, if HBV DNA is ≥500 IU/mL.
- Complete blood count.
- Comprehensive metabolic panel.
- Urine pregnancy test for women of childbearing potential.
- FibroScan test (IHV only) – this test may be conducted within 30 days prior to or on the Day 1 Visit.
- Blood for PAXgene DNA and RNA analysis.
- Blood for storage of plasma, serum, and peripheral blood mononuclear cells (PBMC) for future research purposes.

Study Drug Administration (and Post-Study Drug Assessments):

- Administer first dose of B/F/TAF.
- Dispense study drug supply (remainder of 60-day supply).
- Reinforce study drug instruction: subjects are to take one (1) tablet of B/F/TAF once daily upon awakening with at least 8 oz. of plain water, and without regards to food.
- Dispense Study Drug Diary.
- Collect adverse event information.
- Collect concomitant medication information.
- Instruct subject to bring all study drugs and bottles to each future study visits.

3.2.3 Treatment Assessments

3.2.3.1 Week 4 and 8 Visits (± 7 days)

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs [BP, R, HR, T].
- Collect concomitant medication information.
- Collect adverse event information.
- Evaluate Patient Diary and number of used and unused tablets.
- Plasma HIV-1 RNA.
- Plasma HBV DNA.
- Quantitative HBsAg level.
- Complete blood count.
- Comprehensive metabolic panel.
- Urine pregnancy test for women of childbearing potential.
- Blood for storage of plasma, serum, and PBMCs.
- Dispense study drug supply (30-day supply for Week 4; 60-day supply for Week 8).
- Reinforce study drug instruction: subjects are to take one (1) tablet of B/F/TAF once daily upon awakening with at least 8 oz. of plain water, and without regards to food.
- Instruct subject to bring all study drugs and bottles to each future study visits.

3.2.3.2 Week 12, 24, and 36 Visits (± 2 weeks for Week 12 and Week 36; ± 4 weeks for Week 24)

- Obtain interval medical history.
- Conduct targeted physical examination (if needed), including weight and vital signs [BP, R, HR, T].
- Collect concomitant medication information.
- Collect adverse event information.
- Evaluate Patient Diary and number of used and unused tablets.
- Plasma HIV-1 RNA.
- Plasma HBV DNA.
- Quantitative HBsAg level.
- CD4 cell count.
- Complete blood count.
- Comprehensive metabolic panel.
- Urine pregnancy test for women of childbearing potential.
- Blood for PAXgene RNA analysis.
- Blood for storage of plasma, serum, and PBMCs.

- Dispense study drug supply (90-day supply).
- Reinforce study drug instruction: subjects are to take one (1) tablet of B/F/TAF once daily upon awakening with at least 8 oz. of plain water, and without regards to food.
- Instruct subject to bring all study drugs and bottles to each future study visits.

Additional Week 24 assessments:

- HBV profile.
- FibroScan test (IHV only). This test may be done during the Week 24 visit, or within 2 weeks (before or after) the scheduled Week 24 visit.

3.2.3.3 Week 48 Visit (± 4 weeks): End-of-Study Assessments

This describes the end-of-study assessments for all subjects including those who discontinue study prematurely.

- Obtain interval medical history.
- Conduct complete physical examination, including weight and vital signs [BP, R, HR, T].
- Collect concomitant medication information.
- Collect adverse event information.
- Evaluate Patient Diary and number of used and unused tablets.
- Plasma HIV-1 RNA.
- Plasma HBV DNA.
- Quantitative HBsAg level.
- CD4 cell count.
- HIV-1 genotype/phenotype, if HIV-1 RNA is ≥500 copies/mL.
- HBV genotype and resistance assay, if HBV DNA is ≥500 IU/mL.
- HBV profile.
- Complete blood count.
- Comprehensive metabolic panel.
- Coagulation tests.
- Urine pregnancy test for women of childbearing potential.
- FibroScan test (IHV only). This test may be done during the Visit, or within 2 weeks (before or after) the scheduled Week 48 visit.
- Blood for PAXgene RNA analysis.
- Blood for storage of plasma, serum, and PBMCs.

3.2.4 Early Study Drug Discontinuation Assessments

If the subject discontinues study drug prior to the Week 48 Visit, the subject will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drug

Discontinuation Visit. The subject will be asked to continue attending the scheduled study visits through Week 48, unless informed consent has been withdrawn.

At the Early Study Drug Discontinuation Visit, any evaluation showing abnormal results indicating that there is a possible or probable causal relationship with the study drug, will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to Day 1, or is otherwise explained, or subject has withdrawn consent.

Assessments for the Early Study Drug Discontinuation Visit will follow assessments for Week 48 Visit (see Section 3.1.3.3) except for FibroScan test. A FibroScan test will be done if this Early Study Drug Discontinuation Visit is also an End-of-Study Visit. Additional safety labs may be done at the discretion of the Investigator.

3.2.5 Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the Investigator.
- Unacceptable toxicity, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Lack of efficacy.
- Subject requests to discontinue for any reason.
- Subject noncompliance.
- Pregnancy during the study.
- Development of active tuberculosis infection.
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB).

3.2.6 End of Study

The end of study will be the last patient's last observation (or visit).

3.2.7 Post Study Care

After a subject has completed or terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating physician.

3.2.8 Virologic Failure

HIV-1 virologic failure is defined as virologic rebound or having HIV-1 RNA ≥50 copies/mL at study drug discontinuation, Week 24, or Week 48.

HBV virologic failure is defined as virologic rebound or having HBV DNA ≥29 IU/mL at study drug discontinuation, Week 24, or Week 48. Development of tenofovir resistance plus use of an anti-HBV agent (e.g. entecavir) other than the study drug during the treatment period will also be considered a HBV virologic failure.

3.2.9 Management of Virologic Rebound

Subjects who meet the criteria listed below will be considered to have virologic rebound:

HIV-1 Virologic Rebound:

- At any visit, a rebound in HIV-1 RNA ≥50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
- At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from nadir which is subsequently confirmed at the following scheduled or unscheduled visit.

Following unconfirmed virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA virologic rebound) for confirmation of virologic rebound. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥500 copies/mL, the blood sample from the confirmation test will be the primary sample used for HIV-1 genotypic and phenotypic testing. Subjects with documented non-adherence within 72 hours of the visit may not be tested for resistance. Resistance testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion.

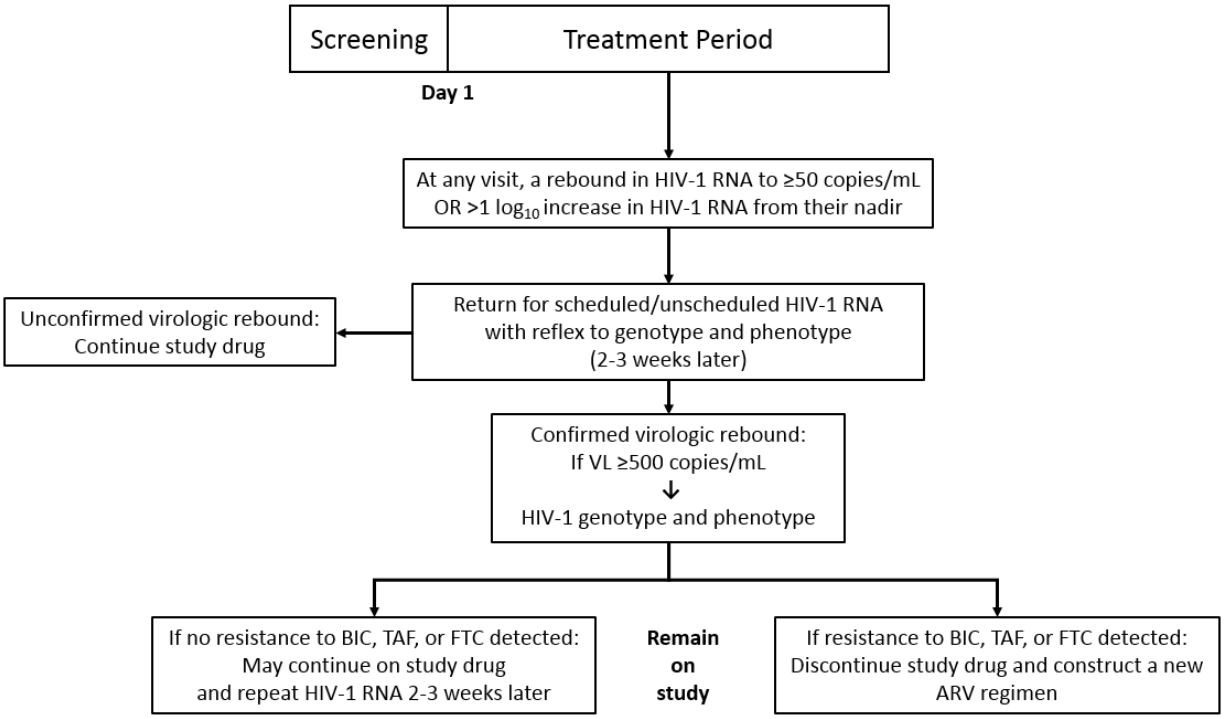
If no resistance is detected, the subject may remain on study drug and a repeat HIV-1 RNA should be repeated (approximately 2 to 3 weeks after date of test with HIV-1 RNA ≥50 copies/mL). Investigator should carefully evaluate the benefits and risk of remaining on the study drug for each individual subject and document this assessment in the medical record.

Subject who are noncompliant on an ongoing basis will be considered for discontinuation per the Investigator's discretion.

For subjects who are off study drug but remain on study, it will be the Investigator's discretion to manage virologic rebound.

Figure 6-1 illustrates the algorithm for the management of subjects who meet the criteria for HIV-1 virologic rebound.

Figure 6-1: Virologic Rebound Schema for HIV-1.



HBV Virologic Rebound:

- At any visit, after achieving HBV DNA <29 IU/mL, a rebound in HBV DNA ≥29 IU/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
- At any visit, a >1 $\log_{10}$ increase in HBV DNA from nadir which is subsequently confirmed at the following scheduled or unscheduled visit.

Following unconfirmed virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HBV DNA virologic rebound) for confirmation of virologic rebound. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HBV DNA is ≥500 IU/mL, the blood sample from the confirmation test will be the primary sample used for HBV genotyping and drug resistance assay. Subjects with documented non-adherence within 72 hours of the visit may not be tested for resistance. After a subject's first postbaseline resistance test, additional testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion.

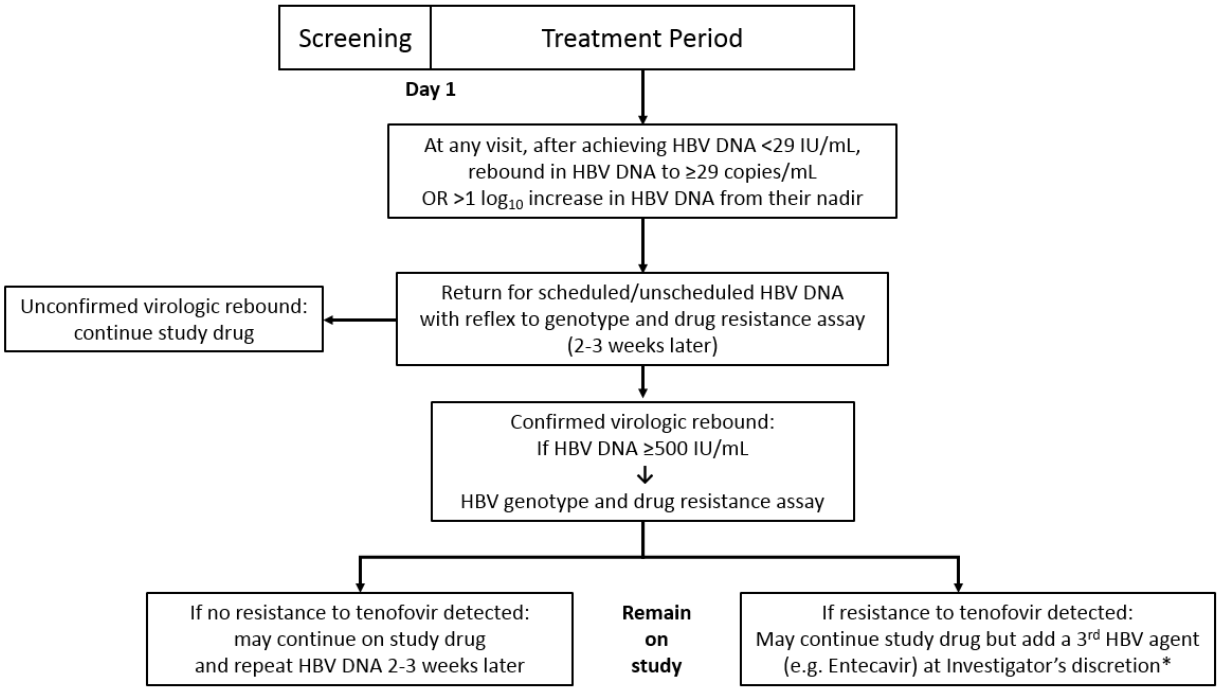
If no resistance is detected, the subject may remain on study drug and a repeat HBV DNA should be repeated (approximately 2 to 3 weeks after date of latest test with HBV DNA ≥29

IU/mL). Investigator should carefully evaluate the benefits and risk of remaining on the study drug for each individual subject and document this assessment in the medical record.

Subject who are noncompliant on an ongoing basis will be considered for discontinuation per the Investigator's discretion.

For subjects who are off study drug but remain on study, it will be the Investigator's discretion to manage virologic rebound.

Figure 6-2 illustrates the algorithm for the management of subjects who meet the criteria for HBV virologic rebound.



*Addition of a "3rd" HBV agent in the setting of tenofovir resistance is considered a HBV virologic failure.

4 DISCUSSION OF DESIGN

This is a multicenter, open-label phase 4 study to evaluate the efficacy, safety, and tolerability of treatment with fixed dosed combination B/F/TAF in adults with HIV-1 and HBV coinfection. This study design allows direct assessment of the safety and efficacy of B/F/TAF in this patient population.

Dose: B/F/TAF is FDA-approved as a fixed dose combination one pill once daily taken orally without regards to food. The approved regimen contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. Efficacy of this FDC B/F/TAF for HIV-1 infection has been established based on four double blind, randomized, active control multicenter studies (two treatment naïve and two switch studies) with 1206 subjects receiving B/F/TAF and combined virologic suppression rate of 91.8% at Week 48 by FDA Snapshot analysis. In these studies, less than 1% discontinued B/F/TAF due to adverse events. The selected dosing is therefore most appropriate for use in this study.

Safety Endpoints: The safety assessments used in this trial are standard assessments for Phase 4 studies evaluating the safety of repeated dosing.

Efficacy Endpoints: Assessment of quantitative plasma HIV-1 RNA and HBV DNA is the standard procedure for determining effectiveness of HIV-1 and HBV therapies, respectively. Both primary and secondary efficacy endpoints use both quantitative HIV-1 RNA and HBV DNA levels as main assessment measure. Additional assessments in this trial (e.g. CD4 count, ALT changes, FibroScan test) are also standard measures in trials with HIV-HBV coinfection.

Length of Assessment: The efficacy and safety assessments will be evaluated through end of study. This period spans a total of 48 weeks for all subjects. This duration of assessment is standard in studies involving HIV-HBV coinfection with primary and secondary endpoints marked at Week 24 and Week 48.

Eligibility Criteria: This is a phase 4 switch study for subjects with HIV-HBV coinfection. Eligibility criteria has been designed to include subjects who in real life may or may not be virally suppressed but would benefit from use of B/F/TAF. This will allow a broader applicability of the study results to a much wider HIV-HBV coinfection population. In addition, recent studies have shown that high efficacy was observed among subjects with baseline M184V or M184I who switched to B/F/TAF with 98% of these subjects achieving HIV-1 RNA <50 copies/mL at their last study visit and with no treatment emergent resistance developing (Andreatta K et al 2019).

5 STUDY POPULATION

The investigators participating in this study have expertise in the diagnosis and management of patients with HIV and HBV. This study will be conducted in the Institute of Human Virology, University of Maryland, Baltimore, MD. Investigators will diagnose subjects with HIV and HBV based on history, physical examination, and laboratory studies.

Participation in this study is voluntary. The nature of the study will be fully explained to each subject during the informed consent process. The subjects will have the opportunity to ask questions. An informed consent document will then be signed by the subject and the person performing the consent discussion, and retained by the investigator according to Good Clinical Practice (GCP). The investigator will retain all documents according to GCP. A copy of the signed informed consent document will be given to the subject.

Eligibility for enrollment will be based on the results of screening utilizing the following inclusion and exclusion criteria.

5.1 Number of Subjects and Subject Selection

This study will enroll approximately 60 subjects who meet the eligibility criteria. We estimate that up to 75 subjects will need to be screened to achieve this enrollment number.

5.2 Inclusion Criteria

Subjects may be included in the study only if they meet **all** of the following criteria:

1. Age 18 years or older at enrollment.
2. Documented HIV-1 infection and currently on a stable regimen for at least 3 months prior to enrollment.
3. No known history of resistance to TAF, FTC, or BIC except M184V and M184I. Those with M184V or M184I mutations will be allowed to enroll in the study.
4. Documented chronic HBV infection, based on any of the following:
    a. Positive HBsAg result or nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) or positive HBeAg on two occasions at least 6 months apart (any combination of these tests performed 6 months apart is acceptable); or
    b. Negative immunoglobulin M (IgM) antibodies to HBV core antigen (anti-HBc IgM) AND a positive results on one of the following tests: HBsAg, HBeAg, or nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) prior to or at screening.

5. No current or prior regimen containing three active anti-HBV agents (drugs active against HBV includes lamivudine [3TC], adefovir [ADV], entecavir [ETV], emtricitabine [FTC], tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide [TAF]).
6. Must have a primary care provider(s) for medical management.
7. Females of childbearing potential must agree to utilize protocol recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix F) from screening and throughout the duration of the study. Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study drug dosing.
8. Male subjects must be willing to abstain from heterosexual intercourse or use a condom throughout the study period.
9. Stated willingness to comply with all study procedures and availability for the duration of the study.
10. Written informed consent must be obtained before any study procedure is performed.

5.3 Exclusion Criteria

Subject meeting any of the following criteria will not be eligible to participate in the study:

1. Females who are pregnant or breastfeeding.
2. Any known allergies to any of the components of B/F/TAF.
3. Treatment with another investigational drug within three months of enrollment.
4. Abnormal hematological and biochemical parameters at screening, including:
    a. Absolute neutrophil count (ANC) < 750 cells/mm^3.
    b. Platelets < 50,000/mm^3.
    c. Hemoglobin < 8.5 g/dL.
    d. AST or ALT of > 5 times upper limit of normal (ULN).
    e. Estimated GFR < 30 mL/min/1.73 m^2.
    f. Total bilirubin > 1.5 times ULN.
5. Previous or current history of malignancy, other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma. Note: Those with a history of malignancy who are in remission for two or more years may be included in the study.
6. An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening.
7. Subjects experiencing decompensated cirrhosis (e.g. ascites, encephalopathy, or variceal bleeding).
8. Acute hepatitis in the 30 days prior to study entry.

9. Active tuberculosis infection.
10. Subjects receiving ongoing therapy with any medications contraindicated for co-administration with B/F/TAF FDC, including but not limited to the following medications in the table below:

Drug Class	Prohibited Agents[#]
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbamazepine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea
Miscellaneous Agents	Mitotane

[#] Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

11. Current alcohol or substance use that in the opinion of the investigator may interfere with subject study compliance.
12. Any other clinical conditions that in the opinion of the investigator would make the subject unsuitable for the study or unable to comply with the dosing requirements.

6 STUDY INTERVENTION

6.1 Study Assignment

This is an open-label study and all eligible subjects will receive fixed dose combination bictegravir/emtricitabine/tenofovir alafenamide taken one pill once daily oral treatment.

6.2 Method of Assignment to Study Intervention

This is an open-label one-arm study.

6.3 Study Drug, Materials, and Supplies

6.3.1 Formulation, Packaging, and Labeling

Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. Each tablet core contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the B/F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline

cellulose. The tablet cores are film-coated with iron oxide red, iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The B/F/TAF tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

6.3.2 Storage Handling and Preparation

Study drugs should be stored at room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs will be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) will not be stored in a container other than the container in which they were supplied.

Bottles will be relabeled by the Investigational Pharmacist as prescribed to each study subject after consent is given and subjects are found to be eligible.

Consideration should be given to handling, preparation, and disposal through measures that will minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling.

6.3.3 Final Disposition of Clinical Supplies

At the end of the study, final study drug supply and accountability records will be reconciled as to drug shipped, drug consumed, and drug remaining. Any discrepancies noted will be documented.

Subject accountability for study drug will be ensured through subject interview (during visits), diaries, and study drug reconciliation at selected visits before dispensing drug supply for the next visit interval. At certain clinic visits, subjects will be asked to return any unused study drug to the study site. Final drug accountability reconciliation will be performed at the subject visit occurring at the end of therapy or at early discontinuation. Unused study drug will be destroyed.

6.4 Dosage Administration

Subjects will be instructed to take study drug (1 tablet of B/F/TAF) orally with at least 8 ounces of plain water once daily in the morning throughout the treatment period. On Day 1, the first dose of the study medication will be administered in clinic after baseline labs have been drawn.

Following initial dosing at Day 1, the study team will provide the subject the remainder of the 30-day study supply to continue on the following day. Subjects will receive additional 30-day supply on Week 4 and Week 8 visits, and 90-day supply on Week 12, 24, and 36 visits.

The study team will be responsible for explaining the correct use of the study drug to the subject, verifying that the instructions are followed properly, maintaining accurate records of study drug dispensing, and collection of all used study drug, including empty drug packaging.

Subjects will be instructed to contact the investigator as soon as possible if a complaint or problem with the study drug exists, so that the situation can be assessed in a timely manner.

6.5 Blinding

This is an open-label noncomparative study. Both the subject and study personnel with direct contact with the subject will know the study treatment that is administered.

6.6 Concomitant Medications

Drug interaction studies have been conducted with B/F/TAF or its components. A complete summary of the pharmacokinetic effects of other drugs on B/F/TAF or its components are found in the BIKTARVY® package Insert (Biktarvy 2018).

Bictegravir is a substrate of CYP3A and UGT1A1. BIC is also an inhibitor of the organic transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro, such that coadministration of BIC with drugs that are substrate of OCT2 and MATE1 (e.g. dofetilide) may increase their plasma concentration. On the other hand, TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), thus, coadministration of drugs that inhibit these enzymes may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of drug transporters P-gp, BCRP, renal transporter MATE1 or OCT2. At clinically relevant concentrations, both BIC and TAF are not an inhibitor of hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1, OAT3, or CYP (including CYP3A) or UGT1A1 enzymes. A list of prohibited medications are listed in **Table 6-1**.

Table 6-1: List of Prohibited Medications

Drug Class	Prohibited Agents[#]
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbamazepine
Antimycobacterials	Rifampin, Rifapentine
GI Motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea
Miscellaneous Agents	Mitotane

[#] Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

7 ADVERSE EVENT AND TOXICITY MANAGEMENT

7.1 Adverse Events

7.1.1 Definition of AE

An adverse event (AE) will be defined as any new unfavorable or unintended sign, symptom, or disease, or change of an existing condition, which occurs during or after treatment, whether or not considered treatment-related. If clinically significant laboratory value lead to or are associated with clinical symptom(s), the diagnosis should be reported as an AE. The lack of drug effect is not any AE in clinical trials because the purpose of the clinical trial is to establish drug effect.

An AE does not include the following:

- Medical or surgical procedure such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing disease, condition, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social, and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not

an AE. Such condition or abnormality is considered a pre-existing and should be documented on the medical history in the CRF.

Prior to enrollment, study personnel will note the occurrence and nature of each subject's medical condition(s) in the Medical History section of the CRF. During the remainder of the study, study personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a subject experiences an AE after the Informed Consent document is signed (entry) but the subject is never assigned to treatment (enrollment), the event will only be reported if the investigator believes that the event may have been caused by a protocol procedure.

Adverse event information will be collected from the time subject signs the informed consent and until the end of the subject's study participation, i.e. Study Week 48 (end-of-study visit) or earlier if consent has been withdrawn. All AEs occurring after the subject has entered the study (that is, after the Informed Consent document is signed) must be recorded in the CRF. If the study drug is discontinued for a subject, study personnel must report and clearly document the circumstances and data leading to any such discontinuation, using designated CRFs. For AEs, the subject should be followed until the event resolves or stabilizes, with frequency of follow-up at the discretion of the investigator.

In case the investigator notices an unanticipated benefit to the subject, study personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit – sleeping longer").

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported for tracking purposes. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

7.1.2 Reporting Procedures for All Adverse Events

The investigators are responsible for monitoring the safety of subjects who have entered this study and noting any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that causes the subject to discontinue the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up will be left to discretion of the investigator.

7.1.3 Adverse Events Severity

The **Division of AIDS (DAIDS) Table for "Grading the Severity of Adult and Pediatric Adverse Events" corrected version 2.1 (July 2017)** will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the DAIDS criteria, the following guidelines should be used to grade severity:

- **Mild (grade 1):** Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- **Moderate (grade 2):** Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicate.
- **Severe (grade 3):** Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- **Life-threatening (grade 4):** Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The term "severe" is a measure of intensity and a severe AE is not necessarily serious.

7.1.4 Adverse Event Relationship to Study Drug

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **Yes (reasonably related):** There is reasonable possibility that the event may have been caused by the study drug.
- **No (not related):** Evidence exist that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provider (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

Ineffective treatment should not be considered as causally related in the context of adverse event reporting.

7.1.5 Adverse Event Expectedness

The investigator will be responsible for determining whether an adverse event is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.2 Serious Adverse Events

7.2.1 Definition of SAE

A serious adverse event (SAE) is defined as an AE that suggests a significant hazard or side effects, regardless of the relationship to study drug. An SAE includes, but may not be limited to, any event that:

- Results in Death.
- Is life threatening. This definition implies that the subject, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly or birth defect.

Medical and scientific judgment will be exercised in deciding whether classification of an AE as serious is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasms; development of drug dependency or drug abuse. Infections resulting from contaminated medicinal product will be considered a medically important event.

7.2.2 Reporting of SAE

All SAE will be reported to the IRB per institutional guidelines. SAEs (regardless of relationship) must be reported to Gilead Pharmacovigilance and Epidemiology (PVE) Office **within fifteen (15) calendar days** of first becoming aware of the event. In turn, the study sponsor will be responsible for reporting any unexpected fatal or life-threatening suspected adverse reactions to the Division of Antiviral Agents at the FDA no later than seven (7) calendar days after receipt of the information. Safety reporting to the FDA will be done within the reporting requirement under 21 CFR 312.32.

The Gilead PVE Office will be notified via fax or email of any potential safety issues or any protocol amendments or changes to the informed consent arising from a safety concern associated with any Gilead products **within fifteen (15) days** of first becoming aware of such event. Except for periodic safety reports, copies of all reports submitted to government agencies that are related to the study, as well as any correspondence with any such authorities will be provided to Gilead Sciences.

Contact information:
Gilead Sciences Inc., Pharmacovigilance and Epidemiology (PVE)
333 Lakeside Drive, Foster City, CA 94404
Fax: (650) 522-5477
Tel: (650) 522-5114
Email: Safety_FC@gilead.com

7.3 Laboratory Tests

Clinical laboratory tests will be performed at the time specified in the Study Schedule (see Section 12: Schedule of Activities). All clinical laboratory assessments will be analyzed through a designated laboratory.

The investigator must further evaluate laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values. Investigators must also document their review of each laboratory report by signing or initialing and dating each report.

Clinically significant laboratory abnormalities will be reported as AEs.

7.4 Reporting of Events to Participants

Any adverse event or serious adverse event that affects the risk/benefit ratio to subjects will prompt a revision to the informed consent document. All subjects will be notified of the additional risk and re-consented at their next visit, or earlier if the situation requires.

7.5 Reporting of Pregnancy

Pregnancy itself is not an adverse event. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information of all pregnancies will be reported to the Gilead PVE via fax or email **within fifteen (15) calendar days** from site awareness of the pregnancy. . The participant will be advised to notify her obstetrician of study agent exposure.

Pregnancy outcome data (e.g., delivery outcome, spontaneous, or elective termination of the pregnancy, presence of absence of birth defects, congenital abnormalities, or other complications) will be reported to the Gilead PVE Office **within fifteen (15) calendar days** of the site awareness on a protocol-specified form.

7.6 Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix C as outlined below.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the **Division of AIDS (DAIDS) Table for "Grading the Severity of Adult and Pediatric Adverse Events" corrected version 2.1 (July 2017).**
- Grade 3 and 4 laboratory abnormalities that are found to be clinically significant should be confirmed by a repeat testing **within 3 calendar days** of awareness of the results and before study drug discontinuation, unless such a delay is not consistent with good medical practice.

7.6.1 Grade 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the Investigator.

7.6.2 Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinical AE or clinically significant laboratory abnormality that is considered unrelated to the study drug, the study drug may be continued.
- For Grade 3 clinical AE or clinically significant laboratory abnormality that is considered to be related to study drug confirmed by repeat test, the study drug should be withheld until the toxicity returns to ≤ Grade 2.
- When restarting study drug following resolution of the adverse event, the study drug should be restarted at full dose.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with study drug and is considered related to the study drug, then the study drug should be permanently discontinued and the subject managed according to local standard of care practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation and study drug may be continued according to the discretion of the Investigator.

7.6.3 Grade 4 Laboratory Abnormality or Clinical Event

- For Grade 4 clinical AE or clinically significant laboratory abnormality confirmed by repeat testing that is considered related to the study drug, the study drug should be permanently discontinued and subject managed according to local standard of care practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. Clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be management according to the algorithm for the new toxicity grade.

- Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to study drug.

7.6.4 On-Treatment ALT Flare and Exacerbation of Hepatitis B Management

On-treatment ALT flare is defined as:

- Confirmed (within 3 days of awareness of initial laboratory results) serum ALT > 2 x Day 1 value and >10 x ULN, with or without associated symptoms.

7.6.4.1 Management of ALT Flare in Subjects Receiving Study Medications

If laboratory results indicate elevation of ALT > 2 x Day 1 value and > 10 x ULN, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.
- If the ALT elevation is confirmed, check labs for plasma HBV DNA reflex to genotype and drug resistance testing, HBV serology, HDV, HAV IgM, and HCV.

Recommend to check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and serum albumin. Based on the results of the confirmatory tests, the following treatment modifications are recommended:

If Normal or Stable Total Bilirubin or INR related to Day 1 Liver Function Test

If ALT levels are elevated (i.e., >2 x Day 1 and >10 x ULN) with normal or stable total bilirubin and INR related to Day 1, the subject may remain on study medication and should be monitored weekly until ALT levels return to normal or Day 1 level. During monitoring, if the ALT values remain persistently elevated, the Investigator has the discretion based on clinical judgment whether to withhold study drug or not.

If Elevated Total Bilirubin or INR related to Day 1 Liver Function Test

If ALT levels are elevated (i.e., >2 x Day 1 and >10 x ULN), with total bilirubin confirmed to be 2 x Day 1 value, and INR level is 0.5 above Day 1, provided both are >ULN, the Investigator should consider discontinuing study medication (unless the safety of the patient is of immediate concern). The subject should be monitored weekly as long as ALT, total bilirubin, and INR values remain elevated or above Day 1 values.

During monitoring, if the ALT values and the liver function tests remain persistently elevated, and no alternative cause other than the study drug has been found, the Investigator should discuss with a member of the Safety Monitoring Committee whether the study drug should be discontinued.

7.6.4.2 Management of Exacerbation of Hepatitis B in Subjects who have Discontinued Study Medication

If laboratory results indicate (1) an ALT elevation >2 x Day 1 and >10 x ULN alone OR associated with (2) abnormal laboratory parameters suggestive of worsening hepatic function (total bilirubin >2 x Day 1, INR >0.5 above Day 1, provided both are > ULN) and the subject is on no post-study therapy for HBV, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.
- Check the following laboratory parameters: serum ALT and AST, bilirubin, INR, and albumin.
- If the ALT elevation is confirmed, check labs for plasma HBV DNA reflex to genotype and drug resistance testing, HBV serology (HBsAg and HBsAb), HDV, HAV IgM, and HCV. If serum HBV DNA is increasing, the Investigator should consider immediate initiation of approved HBV therapy.
- The subject should be followed until laboratory parameters (ALT, total bilirubin, INR) return to normal or Day 1 up to a maximum of 6 months after the initial occurrence of the event.

7.6.5 On-Treatment Hepatitis C Management

If a subject tests positive for HCV RNA at screening or develops signs or symptoms of active hepatitis C, Sponsor recommends that local medical practice be followed at the discretion of the Investigator. Study medications may be continued without dose interruption. Should subject's primary treating physician or the Investigator decide to initiate hepatitis C treatment, drug-drug interaction should be evaluated. Subject should return to the clinic for scheduled or unscheduled follow up visit(s) according to local medical practice for laboratory evaluation.

7.6.6 On-Treatment Hepatitis D Management

If a subject tests positive for HDV at screening or develops signs or symptoms of active hepatitis D, Sponsor recommends that local medical practice be followed at the discretion of the Investigator.

8 QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the U.S. Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standard of GCP; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator must allow study-related monitoring, audits, and inspection by the IRB, sponsor (or designee), government regulatory agencies, and, if applicable, University compliance and quality assurance groups of all trial-related documents and procedures.

The investigator shall prepare and maintain accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations.

The IHV Clinical Research Unit (CRU) will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be addressed.

9 STATISTICAL CONSIDERATIONS

9.1 General Consideration & Populations for Analyses

The primary analysis for efficacy analyses will employ intention-to-treat (ITT) population defined as the full analysis population, which will include all subjects who have received at least 1 dose of the study drug.

The secondary analysis for efficacy analyses will employ a per-protocol (PP) population, which will include all subjects who have received at least one dose of the study drug, and have not committed any major protocol violation, including the violation of key eligibility criteria. In the Week 24 (or Week 48) per-protocol analysis, subjects meeting any of the following criteria will be excluded:

a. Subjects who do not have on-treatment HIV-1 RNA and/or HBV DNA in the Week 24 (or Week 48) analysis window, except when missing data is due to discontinuation of study drug for lack of efficacy.
b. Subjects who were removed from study due to nonadherence to study drug or due to protocol violation by the subject.

9.2 Sample Size Determination

This study is anticipated to screen up to 75 subjects to enroll approximately 60 subjects coinfected with HIV and HBV, who are currently on antiretroviral therapy. The primary analysis endpoint to evaluate treatment efficacy used to compute the sample size is the observed HIV-1 viral suppression rate. A true suppression rate at Week 24 of at least 91% would be considered active in this patient population. An exact binomial test with a 0.05 type I error rate will have 84% power to detect the difference between the null hypothesis proportion (number of suppressed/total number treated) of 0.773 (based on published results) and the research hypothesis proportion of 0.910 (our educated guess on the desired rate of success) when the sample size is 60.

9.2.1 Analysis Objectives

The primary objective of this study is to evaluate the efficacy of FDC B/F/TAF in adults coinfected with both HIV-1 and HBV, after switching from their current antiretroviral regimen, as determined by HIV-1 RNA <50 copies/mL and/or HBV DNA <29 IU/mL at Week 24.

The secondary objectives of the study include evaluation of HIV-1 and HBV viral suppression at Week 48 as well as safety and tolerability at Week 24 and Week 48.

9.2.2 Analysis of the Primary Efficacy Endpoints

The primary endpoints are:

- The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 as defined by the US FDA Snapshot Algorithm.
- The proportion of subjects with plasma HBV DNA <29 IU/mL at Week 24 using the missing = failure method.

9.2.2.1 US FDA Snapshot Algorithm for HIV-1 Efficacy Analyses

The analysis window at Week 24 is defined as from Study Day 140 to Day 196. All HIV-1 RNA data collected on-treatment will be used in the snapshot algorithm. HIV-1 Virologic outcome will be defined as the following categories:

- **HIV-1 Virologic Success:** this includes subject who have the last available HIV-1 RNA < 50 copies/mL in the Week 24 analysis window while on study treatment.
- **HIV-1 Virologic Failure:** this includes subjects who
    a. Have the last available HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window while on study treatment, or
    b. Do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and
        1) Discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or
        2) Discontinue study drug prior to or in the Week 24 analysis window due to reasons other than adverse events (AE), death, or lack of efficacy and have the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug ≥ 50 copies/mL.
- **No HIV-1 Virologic Data in the Week 24 analysis window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:
    a. Discontinuation of the study drug prior to or in the Week 24 analysis window due to AE or death (regardless of whether the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug < 50 copies/mL or not), or
    b. Discontinuation of the study drug prior to or in the Week 24 analysis window due to reasons other than AE, death, or lack of efficacy (e.g., withdrew consent and loss to follow-up) and the last available HIV-1 RNA up to 1 day after the premature discontinuation of the study drug is < 50 copies/mL, or
    c. Missing data during the window but remains on study drug.

9.2.2.2 Missing = Failure Method for HBV Efficacy Analyses

Similarly, the analysis window at Week 24 for HBV DNA outcomes is defined as from Study Day 140 to Day 196. For HBV DNA analysis, this study will use the missing = failure method. HBV virologic outcome will be defined as follows:

- **HBV Virologic Success:** this includes subject who have the last available HBV DNA <29 IU/mL in the Week 24 analysis window while on study treatment.
- **HBV Virologic Failure:** this includes subjects who
    a. Have the last available HBV DNA ≥ 29 IU/mL in the Week 24 analysis window while on study treatment, or
    b. Do not have on-treatment HBV DNA data in the Week 24 analysis window regardless of reason (e.g. discontinued study drug due to AE, death or lack of efficacy; missed Week 24 visit; withdrew consent for any reason).

9.2.3 Analysis of the Secondary Endpoints

The secondary endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA Snapshot Algorithm.
- The proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48 using the missing = failure method.
- Change from baseline in CD4 cell count and percentage at Week 24 and at 48.
- Proportion of subjects with normalized ALT at Week 24 and Week 48.
- Proportion of subjects with HBV e antigen (HBeAg) loss and seroconversion to anti-HBe at Week 24 and Week 48.
- Proportion of subjects with HBV surface antigen (HBsAg) loss and seroconversion to anti-HBs at Week 24 and Week 48.
- Change from baseline in Fibroscan test score at Week 24 and Week 48.

9.2.4 Safety Analyses

All safety analysis will be performed using the intention-to-treat population. All safety data collected on or after the date, that the study drug was first administered up to the end of the subject's study participation will be summarized for the subject in the safety analysis.

The primary safety endpoint is the proportion of subjects who discontinues study drug due to an adverse event.

There is no formal stopping rule for this trial. The toxicity data will be monitored closely through the therapy. Addressing the safety of FDC B/F/TAF, a maximum width 95% confidence

interval (CI) for any adverse event, grade 3 or higher toxicity will be about 28%. For 50 patients on the study, if the true unknown probability of a rare toxicity is 0.05 (5%), the probability of observing one or more toxicities is 0.92 (92%), and for 3% true toxicity rate, it is 78%.

9.2.5 Baseline Descriptive Statistics

Demographics and other baseline characteristics will be summarized by treatment group.

9.2.6 Planned Interim Analyses

No interim analyses are planned for this study.

9.2.7 Subgroup Analyses

For subgroup analyses, the analysis of the efficacy endpoints will be performed and stratified based on age group, sex, race, baseline CD4 count, HBV DNA viral load, baseline HBeAg status, and baseline HBsAg level.

9.2.8 Exploratory Analyses

Exploratory analyses will include assessment of changes in quantitative HBsAg and immune activation markers during study drug treatment. Immune markers includes plasma hsCRP, IL-6, TNF-α, and D-dimer and cellular HLA-DR+CD38+ CD4 and CD8 T lymphocytes. The exploratory analyses will determine group difference in the exploratory endpoints from baseline (Day 1) to Week 24 and Week 48 time points using a paired t-test. All inferential tests will be indicated statistical significance with a P-value of less than 0.05 (two-sided).

10 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

10.1 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. The informed consent form will be IRB-approved and the participant will be asked to read and review the document. The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each subject or legally authorized representative by obtaining the appropriate signatures and dates on the informed consent document before the performance of protocol evaluations or procedures.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Copies of the informed consent documents will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the screening form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Additionally, employees or students will be made aware that employment status or academic standing will not be affected by your participation or non-participation in this study. Students or employees will not be consented by anyone in a supervisory role.

As the majority of the patient populations from which the study participants are drawn are literate, written informed consent will typically be provided during the informed consent process. However, oral consent will be obtained for illiterate participants as consistent with UMB IRB Policy without separate IRB approval for each specific use. At Continuing Reviews, the UMB IRB will be informed of the number of illiterate participants who provided consent verbally. A non-study team witness will be present for the oral consenting process.

10.2 Study Discontinuation and Closure

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. The suspending or terminating party will provide written notification, documenting the reason for study suspension or termination, to the study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor, and regulatory authorities in a timely manner. If the study is prematurely terminated or suspended, the Investigator will promptly inform study

participants, the IRB, and sponsor, and he will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, DSMB, IRB and/or Food and Drug Administration (FDA) as appropriate.

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be entered into the electronic database for future analysis. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the IHV research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the IHV.

10.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at University of Maryland, Institute of Human Virology. With the participant's approval within the consent and as approved by local IRB, de-identified biological samples may be shared with Gilead Sciences, Inc. with the goal of sharing of data. These samples could be used to research immune response to HBV, its complications and other conditions for which individuals with HBV are at increased risk, and to improve treatment. Gilead Sciences, Inc. will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have optional biological specimens for future research stored, in which case they will be destroyed.

When the study is completed, access to study data and/or samples will be provided by Dr. Joel Chua.

10.5 Key Roles and Study Governance

Principal Investigator
Joel Chua, MD; Assistant Professor
University of Maryland, Institute of Human Virology
725 W. Lombard Street
410-706-5704
JChua@ihv.umaryland.edu

10.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Safety Monitoring Committee (SMC) composed of individuals with the appropriate expertise, including experience with the treatment and/or care of those with HIV-1 and HBV. At least two members of the SMC will be independent from

the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The SMC will meet at least semiannually to assess safety and efficacy data. The SMC will provide its input to the study sponsor and Principal Investigator.

10.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring will begin as the first two subjects screen for the clinical trial. This will entail a clinical research nurse providing 100% verification of screening consent and data verification of the first 2 subjects. An independent SMC member will be available for consultation as needed for any medical concerns.

Once subjects begin enrollment, consent and eligibility verification will continue at 100%, with 15% targeted subject data review.

10.8 Data Handling and Record Keeping

10.8.1 Data Collection and Management Responsibilities

All research data and results will be recorded using data collection forms. Source documents will support the data collected and will include, but not limited to; clinical findings and observations, laboratory and test data, hospital medical records, physician or office charts, physician or nursing notes, recorded data from automated instruments, x-rays, etc. Research data will be entered into a secure electronic database. This electronic database tracks all data corrections made by authorized users, providing audit trails for monitoring or query.

10.8.2 Study Records Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP Guideline. All essential documentation for all study subjects are to be maintained by the investigators in a secure storage facility for a minimum of 5 years. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

10.9 Protocol Deviation

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP guidelines. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. When a protocol deviation by the Investigator or his study staff occurs, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations that constitute **Reportable New Information within 5 working days** of identification of the protocol deviation or as prescribed by local IRB requirements. The Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.10 Publication and Data Sharing Policy

This trial is registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed accordingly. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

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APPENDIX A. SCHEDULE OF ACTIVITIES

Study Procedures	Screening (D-90 to -3)	Day 1	Study Week					
			4	8	12	24	36	48[g]
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Complete Medical History	X							
Interval Medical History		X	X	X	X	X	X	X
Administer 1st Dose of Study Drug		X						
Study Drug and Diary Dispensation		X	X	X	X	X	X	
Study Drug Accountability			X	X	X	X	X	X
Clinical Procedures/Assessments								
Complete Physical Exam	X	X						X
Targeted Physical Exam, if needed			X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Adverse event		X	X	X	X	X	X	X
Height	X							
Vital Signs (T, P, R, BP) and Wt	X	X	X	X	X	X	X	X
12-lead ECG	X							
Clinical Laboratory Tests								
Plasma HIV-1 RNA	X[a]	X	X	X	X	X	X	X
Plasma HBV DNA	X[a]	X	X	X	X	X	X	X
Quantitative HBsAg level	X[a]	X	X	X	X	X	X	X
CD4 Cell Count	X[a]	X			X	X	X	X
HBsAg/HBcAb/HBsAb/HBeAg/HBeAb	X[a]					X		X
HIV-1 Genotype/Phenotype[b]		X						X
HBV Resistance Assay[c]		X						X
HBV Genotype[c]		X						
HCV serology	X[a]							
HDV serology	X[a]							
CBC	X[a]	X	X	X	X	X	X	X
CMP	X[a]	X	X	X	X	X	X	X
Coagulation Tests (PT/PTT)	X[a]							X
Fibroscan (IHV only)		X[e]				X[f]		X[f]
Urinalysis	X[a]							
Urine pregnancy test (if WOCP[d])		X	X	X	X	X	X	X
Serum pregnancy test (if WOCP[d])	X							
Research Laboratory Tests								
PAXgene RNA Assay		X			X	X	X	X
PAXgene DNA Assay		X						
PBMC Storage		X	X	X	X	X	X	X
Plasma Storage		X	X	X	X	X	X	X
Serum Storage		X	X	X	X	X	X	X

Legend:

[a] May use outside labs if within 90 days.

[b] If HIV-1 RNA is ≥500 copies/mL

[c] If HBV DNA is ≥500 IU/mL

[d] Woman of childbearing potential

[e] Fibroscan at Baseline (Day 1) may be conducted within 30 days prior to Day 1 Visit.

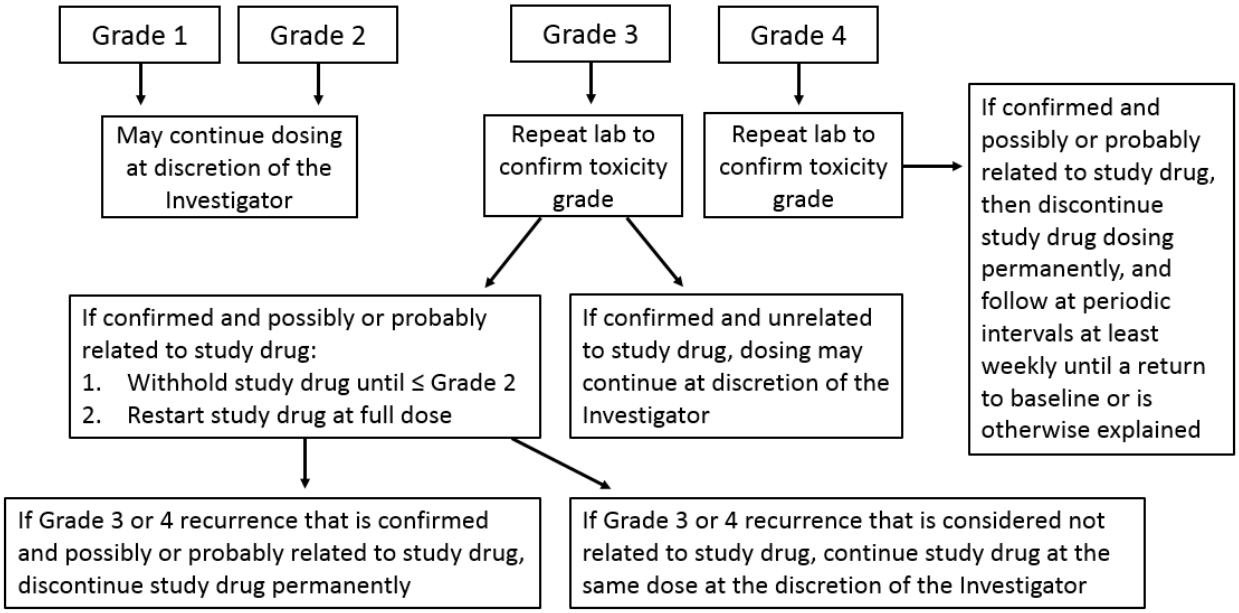
[f] Fibroscan at Week 24 and Week 48, may be conducted 2 weeks before or after the Study Visit.

[g] Week 48 (End of Study) Visit procedures will be used for Early Termination/Subject Withdrawal Visits.

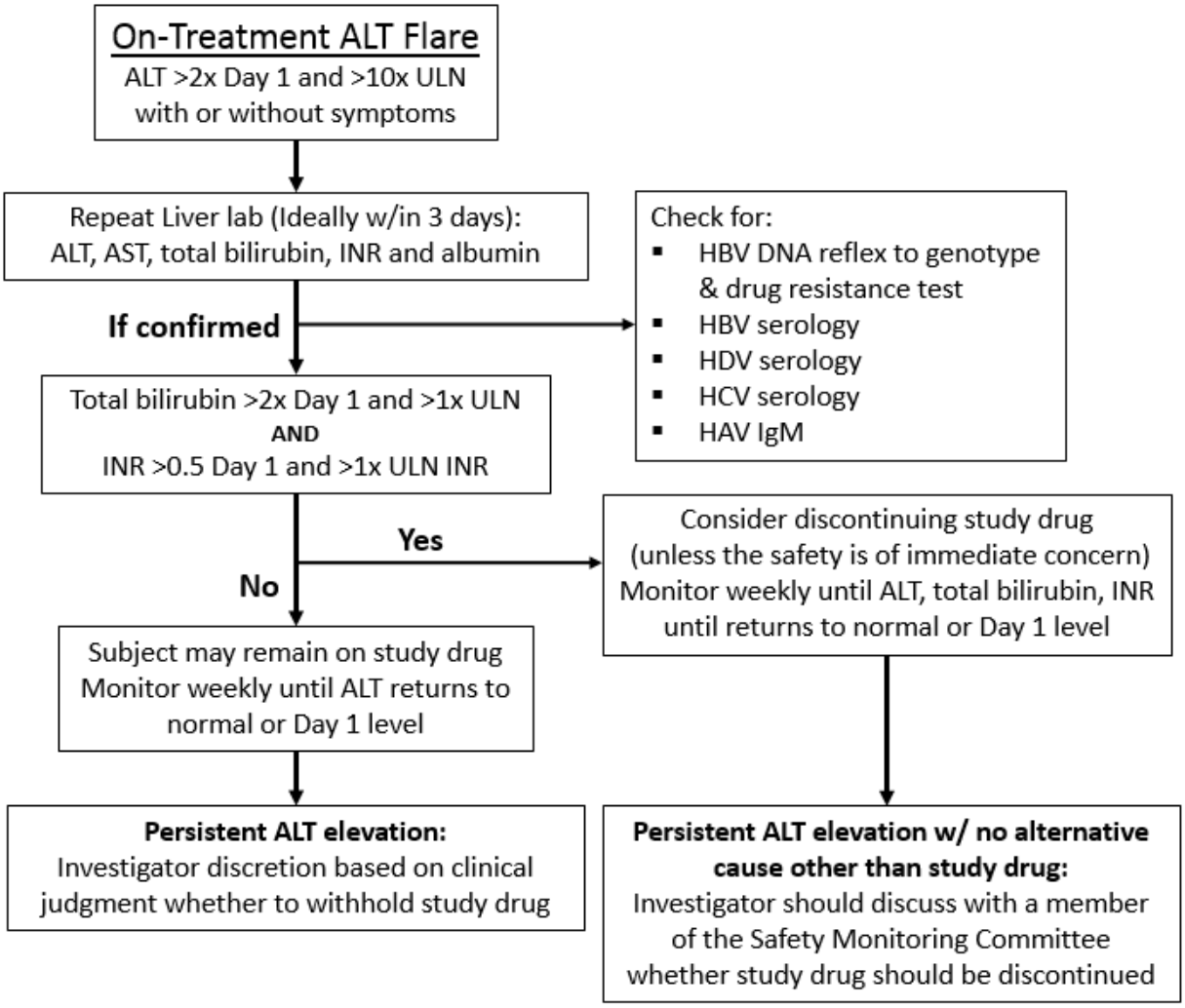
APPENDIX B. PROTOCOL AMENDMENT HISTORY

Version (version date)	Affected Sections	Description of Changes	Brief Rationale
1.1	3.2.2. Day 1 Assessments	Dispense study drug supply from 30-days to up to 60-days	Allow extra study drug to be dispense to subjects on Day 1 to avoid having them ran out before next study visit window.
2.0	5.3 Exclusion Criteria	Clarification on history of malignancy as an exclusion	Allow subjects with history of malignancy that is in remission to be included in this phase 4 study.
3.0	5.2 Inclusion Criteria and Figure 3-1 in Study Schema. Rationale in Section 4. Discussion of Design	Eligibility to allow those with M18V mutation and those who are currently not HIV suppressed to enter the study.	Allows subjects with M184V and M184I mutation or having HIV viral load not suppressed to be included in the study as these does not affect response to B/F/TAF. Rationale added to Section 4. Discussion of Design
4.0	3.1 Study Design, and 3.2 Study Procedures	Change from single center to multicenter study. Fibroscan will only be done in the IHV.	Allow addition of a second site (Philadelphia DOH clinic). Only IHV site has FibroScan to conduct this procedure.

APPENDIX C. MANAGEMENT OF CLINICAL & LABORATORY AEs



APPENDIX D. MANAGEMENT OF ON-TREATMENT ALT FLARES



APPENDIX E. DEFINITION OF STAGE 3 OPPORTUNISTIC ILLNESS IN HIV

Based on CDC Guidelines, Stage 3 HIV/AIDS opportunistic infections are as follows:

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis of esophagus
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (>1 month duration)
7. Cytomegalovirus disease (other than liver, spleen or nodes)
8. Cytomegalovirus retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer(s) (>1 month duration); or bronchitis, pneumonitis or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (>1 month duration)
13. Kaposi's sarcoma
14. Lymphoma, Burkitt's (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary
18. *Mycobacterium tuberculosis*, of any site, pulmonary, disseminated or extrapulmonary
19. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
20. *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia
21. Pneumonia, recurrent
22. Progressive multifocal leukoencephalopathy
23. *Salmonella* septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome attributed to HIV infection

APPENDIX F. DEFINITION OF CHILDBEARING POTENTIAL, CONTRACTIVE REQUIREMENTS & PREGNANCY PRECAUTIONS

Definition of Childbearing Potential

For the purpose of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥54 years of age with cessation of previously occurring menses for ≥12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

Contraception Requirement for Female Subjects

a. Study Drug Effect on Pregnancy and Hormonal Contraception

The effect of B/F/TAF in pregnancy is currently not known. Relevant non-clinical reproductive studies for human pregnancy do not indicate a strong suspicion of human teratogenicity or fetal toxicity. Data from clinical pharmacokinetic interaction studies of B/F/TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception or that the effect on hormonal contraception is insignificant. Please refer to the latest BIKTARVY U.S. package insert for more information.

b. Study Drug Effect on Pregnancy and Hormonal Contraception

To be included in the study, women of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and negative urine pregnancy test on the Day 1 visit prior to enrollment. At the minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This will apply even to women of childbearing potential with infrequent or irregular periods.

Female subject must agree to **at least one** of the following from Screening until end of study:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

OR

- Consistent and correct use of 1 of the following methods of birth control:
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

OR

- Consistent and correct use of hormonal method and one barrier method
  - Barrier methods:
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods:
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Contraceptive Requirements for Male Subjects

Relevant systemic concentrations of the study drug may in theory be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must abstain from heterosexual intercourse or use condoms during treatment and until end of study.

Procedures to Follow in the Event of Pregnancy

Subjects will be instructed to notify the study team if they become pregnant at any time during the study. Subject who become pregnant or who is suspected to be pregnant must report the information to the Investigator and after a thorough assessment, the study drug may be discontinued based on clinical judgment. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the Investigator.