BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets
℞ Only

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY.

Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY

Prior to or when initiating BIKTARVY, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)].*

2.2 Recommended Dosage

BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food in:

- adults and pediatric patients weighing at least 25 kg and estimated creatinine clearance greater than or equal to 30 mL per minute; or

- virologically-suppressed adults with estimated creatinine clearance below 15 mL per minute who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment. BIKTARVY should generally be avoided but may be used in these patients if the potential benefits are considered to outweigh the potential risks [see Use in Specific Populations (8.5) and Clinical Pharmacology (11.3)].

2.3 Not Recommended in Patients with Severe Renal Impairment

BIKTARVY is not recommended in patients with:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute); or
- end stage renal disease (ESRD; estimated creatine clearance below 15 mL per minute) who are not receiving chronic hemodialysis; or
- no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis *[see Dosage and Administration (2.2) and Use in Specific Populations (8.5)]*.

2.4 Not Recommended in Patients with Severe Hepatic Impairment

BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)].*

3 DOSAGE FORMS AND STRENGTHS

Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.

4 CONTRAINDICATIONS

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events *[see Drug Interactions (7.5)]*.

- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY *[see Drug Interactions (7.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) infection before or when initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Loss of therapeutic effect of BIKTARVY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during BIKTARVY therapy; review concomitant medications during BIKTARVY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of BIKTARVY, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs greater than 30 mL per minute, and in virologically suppressed subjects switched to BIKTARVY with eGFRs greater than 50 mL per minute, renal serious adverse events were encountered in less than

1% of subjects treated with BIKTARVY through Week 48 *[see Adverse Reactions (6.1)].* BIKTARVY is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute), or patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis [see Dosage and Administration (2.3), Use in Specific Populations (8.5)].

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of BIKTARVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)].*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adults with No Antiretroviral Treatment History

The primary safety assessment of BIKTARVY was based on data from two randomized, double-blind, active-controlled trials, Trial 1489 and Trial 1490, that enrolled 1274 HIV-1 infected adult subjects with no antiretroviral treatment history - through Week 144. After Week 144, subjects received open-label BIKTARVY in an optional extension phase for an additional

96 weeks (end of study). A total of 634 and 1025 subjects received one tablet of BIKTARVY once daily during the double-blind (Week 144) and extension phases, respectively *[see Clinical Studies (13.2)]*.

The most common adverse reactions (all Grades) reported in at least 5% of subjects in the BIKTARVY group in either Trial 1489 or Trial 1490 were diarrhea, nausea, and headache. The proportion of subjects who discontinued treatment through Week 144 with BIKTARVY, abacavir [ABC]/dolutegravir [DTG]/ lamivudine [3TC]), or DTG + FTC/TAF, due to adverse events, regardless of severity, was 1%, 2%, and 2%, respectively. Table 1 displays the frequency of adverse reactions (all Grades) greater than or equal to 2% in the BIKTARVY group.

Table 1 Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Adults with No Antiretroviral Treatment History Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		Trial 1490	
Adverse Reactions	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Diarrhea	6%	4%	3%	3%
Nausea	6%	18%	3%	5%
Headache	5%	5%	4%	3%
Fatigue	3%	4%	2%	2%
Abnormal dreams	3%	3%	<1%	1%
Dizziness	2%	3%	2%	1%
Insomnia	2%	3%	2%	<1%
Abdominal distention	2%	2%	1%	2%

a. Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in > 1% of subjects treated with BIKTARVY.

Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression.

Suicidal ideation, suicide attempt, and depression suicidal occurred in 2% of subjects administered BIKTARVY; these events occurred primarily in subjects with a preexisting history of depression, prior suicide attempt or psychiatric illness.

The majority (84%) of adverse events associated with BIKTARVY were Grade 1.

Adverse reactions in the open-label extension phases of Trials 1489 and 1490 were similar to those observed in subjects administered BIKTARVY in the Week 144 analysis.

Clinical Trials in Virologically Suppressed Adults

The safety of BIKTARVY in virologically-suppressed adults was based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial (Trial 1844) in which virologically-suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically-suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY (Trial 1878). Overall, the safety profile in virologically-suppressed adult subjects in Trials 1844 and 1878 was similar to that in subjects with no antiretroviral treatment history *[see Clinical Studies (13.3)]*.

Clinical Trial in Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

The safety of FTC and TAF (components of BIKTARVY) was evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). The most commonly reported adverse reaction (adverse event assessed as causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 65% of subjects and the most common serious adverse events were pneumonia (15%), fluid overload (7%), hyperkalemia (11%) and osteomyelitis (7%). Overall 7% of subjects permanently discontinued treatment due to an adverse event. In an extension phase of Trial 1825 in which 10 subjects switched to BIKTARVY for 48 weeks, the safety findings were similar to those in the initial phase of the open-label trial [see Use in Specific Populations (8.5), Clinical Studies (13.3)].

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving BIKTARVY in Trials 1489 and 1490 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Subjects Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		**Trial 1490**	
Laboratory Parameter Abnormality[a]	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Amylase (>2.0 x ULN)	3%	4%	3%	4%
ALT (>5.0 × ULN)	2%	2%	3%	1%
AST (>5.0 × ULN)	5%	3%	2%	3%
Creatine Kinase (≥10.0 × ULN)	8%	8%	6%	4%
Neutrophils (<750 mm^3)	3%	4%	3%	2%
LDL-cholesterol (fasted) (>190 mg/dL)	5%	5%	4%	6%
Lipase (> 3.0 x ULN)[b]	2%	2%	<1%	2%
GGT (>5.0 x ULN)	2%	2%	1%	1%

ULN = Upper limit of normal

a. Frequencies are based on treatment-emergent laboratory abnormalities.
b. Lipase test performed only in subjects with serum amylase > 1.5 x ULN.

Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (11.2)]*. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 144. In Trials 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.11 (0.03, 0.19) mg per dL from baseline to Week 144 in the BIKTARVY group and was similar to the comparator groups who received ABC/DTG/3TC, or DTG + FTC/TAF. There were no discontinuations due to renal adverse events through Week 144 in BIKTARVY clinical trials.

Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 17% of subjects administered BIKTARVY through Week 144. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) (12%) and Grade 2 (1.5 to 2.5 x ULN) (4%). Graded bilirubin increases in the ABC/DTG/3TC, and DTG + FTC/TAF groups, were 7% and 8%, respectively. Increases were primarily Grade 1 (5% ABC/DTG/3TC and
7% DTG + FTC/TAF) or Grade 2 (2% ABC/DTG/3TC and 2% DTG + FTC/TAF). There were no discontinuations due to hepatic adverse events through Week 144 in BIKTARVY clinical studies.

Clinical Trials in Pediatric Subjects

The safety of BIKTARVY was evaluated in HIV-1 infected virologically-suppressed subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=50) through Week 24 (cohort 2) in an open label clinical trial (Trial 1474) *[see Clinical Studies (13.4)]*. No new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. Adverse reactions were reported in 10% of pediatric subjects. The majority (85%) of adverse reactions were Grade 1. No Grade 3 or 4 adverse reactions were reported. The adverse reaction reported by more than one subject (regardless of severity) was abdominal pain (n=2). One subject (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single subjects were similar to those seen in adults.

6.2 Postmarketing Experience

The following events have been identified during post approval use of BIKTARVY or products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders

Angioedema, Stevens-Johnson syndrome/toxic epidermal necrolysis, and urticaria.

7 DRUG INTERACTIONS

7.1 Other Antiretroviral Medications

Because BIKTARVY is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Comprehensive information regarding potential drug-drug interactions with other antiretroviral medications is not provided because the safety and efficacy of concomitant HIV-1 antiretroviral therapy is unknown.

7.2 Potential for BIKTARVY to Affect Other Drugs

BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations (see Table 3).

7.3 Potential Effect of Other Drugs on One or More Components of BIKTARVY

BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of therapeutic effect of BIKTARVY and development of resistance *[see Clinical Pharmacology (11.3)]*.

The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC.

TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF *[see Clinical Pharmacology (11.3)]*. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of BIKTARVY and development of resistance (see Table 3).

7.4 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*.

7.5 Established and Potentially Significant Drug Interactions

Table 3 provides a listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies. The drug interactions described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY *[see Contraindications (4), Warnings and Precautions (5.2), and Clinical Pharmacology (11.3)]*.

Table 3 Established and Potentially Significant[a] Drug Interactions: Alteration in Regimen May be Recommended

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: dofetilide	↑ Dofetilide	Coadministration is contraindicated due to the potential for serious and/or life-threatening events associated with dofetilide therapy *[see Contraindications (4)]*.
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Coadministration with alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin[c] rifampin[c,d] rifapentine	↓ BIC ↓ TAF	Coadministration with rifampin is contraindicated due to the effect of rifampin on the BIC component of BIKTARVY *[see Contraindications (4)]*. Coadministration with rifabutin or rifapentine is not recommended.
Herbal Products: St. John's wort[e]	↓ BIC ↓ TAF	Coadministration with St. John's wort is not recommended.
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements[c] Cation-containing antacids or laxatives[c] Sucralfate Buffered medications	↓ BIC	Antacids containing Al/Mg: BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended. Supplements or antacids containing Calcium or Iron: BIKTARVY and supplements or antacids containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing calcium or iron is not recommended.
Metformin	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

a. Table is not all inclusive.
b. ↑ = Increase, ↓ = Decrease.
c. Drug-drug interaction study was conducted with either BIKTARVY or its components as individual agents.
d. Strong inducer of CYP3A and P-gp, and inducer of UGT1A1.
e. The induction potency of St. John's wort may vary widely based on preparation.

7.6 Drugs without Clinically Significant Interactions with BIKTARVY

Based on drug interaction studies conducted with BIKTARVY or the components of BIKTARVY, no clinically significant drug interactions have been observed when BIKTARVY is combined with the following drugs: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy.

Risk Summary

There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects (NTDs) *(see Data)*. Discuss the benefit-risk of using BIKTARVY with individuals of childbearing potential, particularly if pregnancy is being planned. Bictegravir (BIC) and tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women reported to the Antiviral Pregnancy Registry (APR). Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of BIKTARVY at exposures that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended human dose (RHD) (*see Data*). During organogenesis, systemic exposures (AUC) 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 2 (rats) and 78 times (rabbits) the exposure at the RHD of BIKTARVY. In rat pre/postnatal development studies, maternal systemic exposures (AUC) were 30 times (BIC), 60 times (FTC), and 19 times (TDF) the exposures of each component in humans at the RHD.

Data

Human Data

Bictegravir: Data from an observational study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address this risk with BIC.

Emtricitabine: Based on prospective reports to the APR of 3,406 exposures to FTC-containing regimens during pregnancy resulting in live births (including 2,326 exposed in the first trimester and 1,080 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of

2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.7% to 3.0%) with first trimester exposure to FTC-containing regimens and 2.0% (95% CI: 1.3% to 3.1%) with the second/third trimester exposure to FTC-containing regimens.

Animal Data

Bictegravir: BIC was administered orally to pregnant rats (5, 30, or 300 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) on gestation days 7 through 17, and 7 through 19, respectively. No adverse embryo-fetal effects were observed in rats and rabbits at BIC exposures (AUC) of up to approximately 36 (rats) and 0.6 (rabbits) times the exposure in humans at the RHD of BIKTARVY. Spontaneous abortion, increased clinical signs [fecal changes, thin body, and cold-to-touch], and decreased body weight were observed at a maternally toxic dose in rabbits (1000 mg/kg/day; approximately 1.4 times higher than human exposure at the RHD).

In a pre/postnatal development study, BIC was administered orally to pregnant rats (up to 300 mg/kg/day) from gestation days 6 to lactation/post-partum day 24. No significant adverse effects were observed in the offspring exposed daily from before birth (*in utero*) through lactation at maternal and pup exposures (AUC) of approximately 30 and 11 times higher, respectively, than human exposures at the RHD.

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the RHD.

In a pre/postnatal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the RHD.

Tenofovir alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures of approximately 2 (rats) and 78 (rabbits) times higher than the exposure in humans at the recommended daily dose of BIKTARVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 55 (rats) and 86 (rabbits) times higher than human tenofovir exposures at the RHD. Since TAF is rapidly converted to tenofovir and lower tenofovir exposures in rats and mice were observed after TAF administration compared to TDF administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 12 [19] times higher than the exposures in humans at the RHD of BIKTARVY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. Based on published data, FTC has been shown to be present in human breast milk. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is unknown if TAF is present in animal milk.

Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving BIKTARVY.

Data

Animal Data

Bictegravir: BIC was detected in the plasma of nursing rat pups in the pre/postnatal development study (post-natal day 10), likely due to the presence of BIC in milk.

Tenofovir alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.3 Pediatric Use

The safety and effectiveness of BIKTARVY for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indications and Usage (1) and Dosage and Administration (2.2)]*.

Use of BIKTARVY in pediatric patients between the ages of 6 to less than 18 years and weighing at least 25 kg is supported by trials in adults and by an open-label trial in virologically-suppressed pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg receiving BIKTARVY through Week 48 (cohort 1 of Trial 1474, N=50) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg receiving BIKTARVY through Week 24 (cohort 2 of Trial 1474, N=50). The safety and efficacy of BIKTARVY in these pediatric subjects was similar to that in adults, and there was no clinically significant change in exposure for the components of BIKTARVY *[see Adverse Reactions (6.1), Clinical Pharmacology (11.3), and Clinical Studies (13.4)]*.

Safety and effectiveness of BIKTARVY in pediatric patients weighing less than 25 kg have not

been established.

8.4 Geriatric Use

Clinical trials in virologically-suppressed subjects (Trials 4449, 1844, and 1878) included 111 subjects aged 65 years and over who received BIKTARVY, including 86 patients from an open-label, single-arm trial of subjects aged 65 years and over who were switched from their previous antiretroviral regimen to BIKTARVY [see Clinical Studies (13.3)]. Of the total number of BIKTARVY-treated patients in these trials, 100 (90%) were 65 to 74 years of age, and 11 (10%) were 75 to 84 years of age. No overall differences in safety or effectiveness were observed between elderly subjects and adults between 18 and less than 65 years of age, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.5 Renal Impairment

The pharmacokinetics, safety, virologic and immunologic responses of FTC and TAF (components of BIKTARVY) were evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL /min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY and all remained virologically suppressed for 48 weeks [see Adverse Reactions (6.1), Clinical Pharmacology (11.3), Clinical Studies (13.3)].

No dosage adjustment of BIKTARVY is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute, or in virologically-suppressed adults with ESRD (estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment *[see Dosage and Administration (2.3)].*

BIKTARVY is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL per minute, by Cockcroft-Gault), or patients with ESRD (estimated creatinine clearance below 15 mL per minute) who are not receiving chronic hemodialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis, as the safety and/or efficacy of BIKTARVY has not been established in these populations [see Dosage and Administration (2.3), Warnings and Precautions (5.4) and Clinical Pharmacology (11.3)].

8.6 Hepatic Impairment

No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, BIKTARVY is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (11.3)]*.

9 OVERDOSAGE

No data are available on overdose of BIKTARVY in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with BIKTARVY consists of general

supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

10 DESCRIPTION

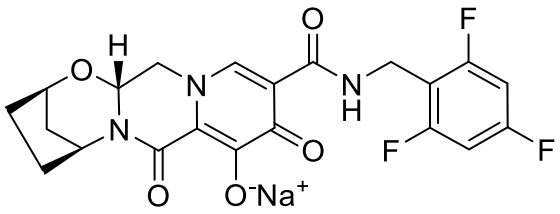
BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

- BIC is an integrase strand transfer inhibitor (INSTI).
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir: The chemical name of bictegravir sodium is 2,5-Methanopyrido[1’,2’:4,5]pyrazino[2,1-*b*][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-*N*-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2*R*,5*S*,13a*R*)-.

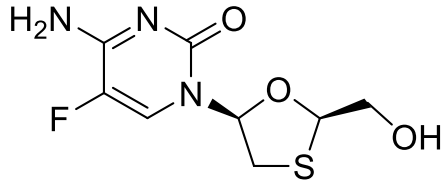
Bictegravir sodium has a molecular formula of $C_{21}H_{17}F_3N_3NaO_5$ and a molecular weight of 471.4 and has the following structural formula:



Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

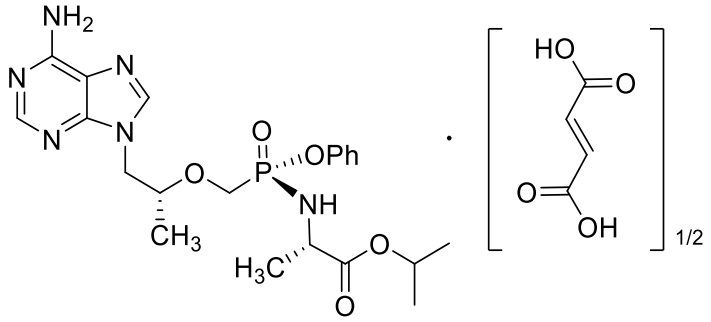
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2 and has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.5 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

BIKTARVY is a fixed dose combination of antiretroviral drugs bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) *[see Microbiology (11.4)]*.

11.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc trial in 48 healthy subjects, BIC at doses 1.5 and 6 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval. In a thorough QT/QTc trial in 48 healthy subjects, 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.

Effects on Serum Creatinine

Mean change from baseline in serum creatinine in healthy subjects who received 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. BIC did not have a significant effect on the estimated creatinine clearance or on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol).

11.3 Pharmacokinetics

The pharmacokinetic (PK) properties of BIKTARVY components are provided in Table 4. The multiple dose PK parameters of BIKTARVY components (based on population pharmacokinetic analysis) are provided in Table 5.

Table 4 Pharmacokinetic Properties of the Components of BIKTARVY

		Bictegravir (BIC)	Emtricitabine (FTC)	Tenofovir Alafenamide (TAF)
Absorption				
T_{max} (h)[a]		2.0–4.0	1.5–2.0	0.5–2.0
Effect of high-fat meal (relative to fasting)[b]	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 proteins		>99	<4	~80
Blood-to-plasma ratio		0.64	0.6	1.0
Elimination				
$t_{1/2}$ (h)[c]		17.3 (14.8, 20.7)	10.4 (9.0, 12.0)	0.51 (0.45, 0.62)[c]
Metabolism				
Metabolic pathway(s)		CYP3A UGT1A1	Not significantly metabolized	Cathepsin A[d] (PBMCs) CES1 (hepatocytes)
Excretion				
Major route of elimination		Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[e]		35	70	<1
% of dose excreted in feces[e]		60.3	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values reflect administration of BIKTARVY with or without food.

b. Values refer to geometric mean ratio [high-fat meal/ fasting] in PK parameters and (90% confidence interval). High fat meal is approximately 800 kcal, 50% fat.

c. $t_{1/2}$ values refer to median (Q1, Q3) terminal plasma half-life. Note that the active metabolite of TAF, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. *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 CES1 in hepatocytes.

e. Dosing in mass balance studies: single dose administration of [^{14}C] BIC; single dose administration of [^{14}C] FTC after multiple dosing of FTC for ten days; single dose administration of [^{14}C] TAF.

Table 5 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Adults

Parameter Mean (CV%)	Bictegravir	Emtricitabine	Tenofovir Alafenamide
C_{max} (microgram per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (microgram•h per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (microgram per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV=Coefficient of Variation; NA=Not Applicable

Specific Populations

Patients with Renal Impairment

No clinically relevant differences in the pharmacokinetics of BIC, TAF, or its metabolite tenofovir were observed between subjects with severe renal impairment (estimated creatinine clearance of 15 to less than 30 mL per minute, by Cockcroft-Gault method) and healthy subjects in Phase 1 studies. In a separate Phase 1 study of FTC alone, FTC exposures were increased in subjects with severe renal impairment.

The pharmacokinetics of BIC, FTC and TAF were evaluated in a subset of HIV-1 infected virologically-suppressed subjects with ESRD (estimated creatinine clearance less than 15 mL per minute, by Cockcroft-Gault method) receiving chronic hemodialysis in Trial 1825.

Exposures of emtricitabine and tenofovir in 12 patients with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis who received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet were significantly higher than in patients with normal renal function. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function.

There were no new safety issues identified in patients with end stage renal disease on chronic haemodialysis receiving emtricitabine and tenofovir alafenamide, in combination with elvitegravir and cobicistat as a fixed- dose combination tablet.

Although there were no new safety issues identified, the implications of increased emtricitabine exposure remain uncertain.

Median (minimum, maximum) BIC Ctrough values in subjects (n=7) with ESRD who received BIKTARVY were 846 ng/mL (288, 1810) compared to 2540 ng/mL (757, 6499) in subjects (N=584) with normal renal function. Despite significantly lower BIC Ctrough values in the virologically-suppressed ESRD population, virologic suppression was maintained [see Use in Specific Populations (8.5), Clinical Studies (13.3)].

Patients with Hepatic Impairment

Bictegravir: Clinically relevant changes in the pharmacokinetics of BIC were not observed in subjects with moderate (Child-Pugh Class B) hepatic impairment.

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of TAF or its metabolite tenofovir were not observed in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.6)]*.

Hepatitis B and/or Hepatitis C Virus Coinfection

The pharmacokinetics of BIC, FTC, and TAF have not been evaluated in subjects coinfected with hepatitis B and/or C virus.

Geriatric Patients

The pharmacokinetics of BIC, FTC, and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 3 trials of BIKTARVY showed that age did not have a clinically relevant effect on exposures of BIC and TAF up to 74 years of age *[see Use in Specific Populations (8.4)]*.

Pediatric Patients

Mean BIC C_{trough} was lower in 50 pediatric patients aged 12 to less than 18 years and weighing at least 35 kg who received BIKTARVY in Trial 1474 relative to adults following administration of BIKTARVY, but was not considered clinically significant based on exposure-response relationships; exposures of FTC and TAF in these pediatric patients were similar to those in adults (Table 6).

Table 6 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 12 to less than 18 years.

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	6.24 (27.1)	2.69 (34.0)	0.133 (70.2)
AUC_{tau} (microgram•h per mL)	89.1 (31.0)	13.6 (21.7)	0.196 (50.3)
C_{trough} (microgram per mL)	1.78 (44.4)	0.064 (25.0)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 1 of Trial 1474 (n=50 for BIC; n=49 for TAF).

b. From Intensive PK analysis of cohort 1 of Trial 1474 (n=24).

Mean BIC C_{max}, and exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 50 pediatric patients between the ages of 6 to less than 12 years and weighing at least 25 kg who received BIKTARVY in Trial 1474 were higher than exposures in adults; however, the increase was not

considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 7) *[see Use in Specific Populations (8.3)]*.

Table 7 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 6 to less than 12 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	9.46 (24.3)	3.89 (31.0)	0.205 (44.6)
AUC_{tau} (microgram•h per mL)	128 (27.8)	17.6 (36.9)	0.278 (40.3)
C_{trough} (microgram per mL)	2.36 (39.0)	0.227 (323)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 2 of Trial 1474 (n=50 for BIC; n=47 for TAF).

b. From Intensive PK analysis of cohort 2 of Trial 1474 (n=25 except n=24 for C_{trough}).

Race and Gender

No clinically relevant changes in the pharmacokinetics of BIC, FTC, and TAF were observed based on gender or race.

Drug Interaction Studies

As BIKTARVY is a complete regimen for the treatment of HIV-1 infection, comprehensive information regarding potential drug-drug interactions with other antiretroviral agents is not provided.

BIC is a substrate of CYP3A and UGT1A1.

BIC is an inhibitor of OCT2 and MATE1. At clinically relevant concentrations, BIC is not an inhibitor of hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1 and OAT3, or CYP (including CYP3A) or UGT1A1 enzymes.

TAF is a substrate of P-gp and BCRP.

At clinically relevant concentrations, TAF is not an inhibitor of drug transporters P-gp, BCRP, hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1, OAT3, OCT2, MATE1, or CYP (including CYP3A) or UGT1A1 enzymes.

Drug interaction studies were conducted with BIKTARVY or its components. Tables 8 and 9 summarize the pharmacokinetic effects of other drugs on BIC and TAF, respectively. Table 10 summarizes the pharmacokinetic effects of BIKTARVY or its components on other drugs.

Effect of Other Drugs on BIKTARVY Components

Table 8 Effect of Other Drugs on BIC[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Ledipasvir/ Sofosbuvir (fed)	90/400 once daily	75 once daily	0.98 (0.94, 1.03)	1.00 (0.97, 1.03)	1.04 (0.99, 1.09)
Rifabutin (fasted)	300 once daily	75 once daily	0.80 (0.67, 0.97)	0.62 (0.53, 0.72)	0.44 (0.37, 0.52)
Rifampin (fed)	600 once daily	75 single dose	0.72 (0.67, 0.78)	0.25 (0.22, 0.27)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir (fed)	400/100/100+100 voxilaprevir[b] once daily	50 once daily	0.98 (0.94, 1.01)	1.07 (1.03, 1.10)	1.10 (1.05, 1.17)
Voriconazole (fasted)	300 twice daily	75 single dose	1.09 (0.96, 1.23)	1.61 (1.41, 1.84)	NA
Maximum strength antacid (simultaneous administration, fasted)	20 mL[c] single dose (oral)	50 single dose	0.20 (0.16, 0.24)	0.21 (0.18, 0.26)	NA
Maximum strength antacid (2 h after BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.93 (0.88, 1.00)	0.87 (0.81, 0.93)	NA
Maximum strength antacid (2 h before BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.42 (0.33, 0.52)	0.48 (0.38, 0.59)	NA
Maximum strength antacid (simultaneous administration, fed[d])	20 mL[c] single dose (oral)	50 single dose	0.51 (0.43, 0.62)	0.53 (0.44, 0.64)	NA
Calcium carbonate (simultaneous administration, fasted)	1200 single dose	50 single dose	0.58 (0.51, 0.67)	0.67 (0.57, 0.78)	NA
Calcium carbonate (simultaneous administration, fed[d])	1200 single dose	50 single dose	0.90 (0.78, 1.03)	1.03 (0.89, 1.20)	NA
Ferrous fumarate (simultaneous administration, fasted)	324 single dose	50 single dose	0.29 (0.26, 0.33)	0.37 (0.33, 0.42)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Ferrous fumarate (simultaneous administration, fed[d])	324 single dose	50 single dose	0.75 (0.65, 0.87)	0.84 (0.74, 0.95)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

c. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

d. Reference treatment administered under fasted conditions.

Table 9 Effect of Other Drugs on TAF[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 single dose[b]	0.43 (0.36, 0.51)	0.46 (0.40, 0.54)	NA
Ledipasvir/sofosbuvir	90/400 once daily	25 once daily	1.17 (1.00, 1.38)	1.27 (1.19, 1.34)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 +100 voxilaprevir[c] once daily	25 once daily	1.28 (1.09, 1.51)	1.57 (1.44, 1.71)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with emtricitabine/tenofovir alafenamide.

c. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Effect of BIKTARVY Components on Other Drugs

Table 10 Effect of Components of BIKTARVY on Other Drugs[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Ledipasvir	90/400 once daily	75 once daily	25 once daily	0.85 (0.81, 0.90)	0.87 (0.83, 0.92)	0.90 (0.84, 0.96)
Sofosbuvir				1.11 (1.00, 1.24)	1.07 (1.01, 1.13)	NA
GS-331007[b]				1.10 (1.07, 1.13)	1.11 (1.08, 1.14)	1.02 (0.99, 1.06)
Metformin	500 twice daily	50 once daily	25 once daily	1.28 (1.21, 1.36)	1.39 (1.31, 1.48)	1.36 (1.21, 1.53)
Midazolam	2 single dose	50 once daily	25 once daily	1.03 (0.87, 1.23)	1.15 (1.00, 1.31)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	75 once daily	-	1.23 (1.14, 1.32)	1.08 (1.05, 1.10)	1.10 (1.05, 1.15)
Norgestrel				1.15 (1.10, 1.21)	1.13 (1.07, 1.19)	1.14 (1.06, 1.22)
Ethinyl estradiol				1.15 (1.03, 1.27)	1.04 (0.99, 1.10)	1.05 (0.95, 1.14)
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	-	25 once daily[c]	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02 (0.92, 1.12)
Sertraline	50 single dose	-	10 once daily[d]	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NA
Sofosbuvir	400/100/100+ 100[e] once daily	50 once daily	25 once daily	1.14 (1.04,1.25)	1.09 (1.02, 1.15)	NA
GS-331007[b]				1.03 (0.99,1.06)	1.03 (1.00,1.06)	1.01 (0.98, 1.05)
Velpatasvir				0.96 (0.91,1.01)	0.96 (0.90, 1.02)	0.94 (0.88, 1.01)
Voxilaprevir				0.90 (0.76, 1.06)	0.91 (0.80, 1.03)	0.97 (0.88, 1.06)

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.
b. The predominant circulating nucleoside metabolite of sofosbuvir.
c. Study conducted with emtricitabine/tenofovir alafenamide.
d. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

11.4 Microbiology

Mechanism of Action

Bictegravir: BIC inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an 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.

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, 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 polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF 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.

Antiviral Activity in Cell Culture

The triple combination of BIC, FTC, and TAF was not antagonistic with respect to antiviral activity in cell culture.

Bictegravir: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. In MT-4 cells (human lymphoblastoid T-cell line) acutely infected with HIV-1 IIIB, the mean 50% effective concentration (EC_{50}) was 2.4±0.4 nM, and the protein-adjusted EC_{95} value was
361 nM (0.162 micrograms per mL). BIC displayed antiviral activity in activated PBMCs against clinical isolates of HIV-1 representing groups M, N, and O, including subtypes A, B, C, D, E, F, and G, with a median EC_{50} value of 0.55 nM (range <0.05 to 1.71 nM). The EC_{50} value against a single HIV-2 isolate was 1.1 nM.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. In PBMCs acutely infected with HIV-1 subtypes A, B, C, D, E, F, and G, the median EC_{50} value for FTC was 9.5 nM (range 1 to 30 nM) and against HIV-2 was 7 nM.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.1 to 12 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.9 to 2.6 nM).

Resistance

In Cell Culture

Bictegravir: HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. In one selection with BIC, a virus pool emerged expressing amino acid substitutions M50I and R263K in the HIV-1 integrase. M50I, R263K, and M50I+R263K substitutions, when introduced into a wild-type virus by site-directed mutagenesis, conferred 1.3-, 2.2-, and 2.9-fold reduced susceptibility to BIC, respectively. In a second selection, emergence of amino acid substitutions T66I and S153F was detected, and 0.4-, 1.9-, and 0.5-fold reductions in BIC susceptibility were observed with T66I, S153F, and T66I+S153F, respectively. In addition, S24G and E157K substitutions emerged during the selection process.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

In Subjects with No Antiretroviral Treatment History: Pooled results of genotypic resistance analyses were performed on paired baseline and on-treatment HIV-1 isolates from subjects receiving BIKTARVY in Trials 1489 and 1490 through Week 144 of the double-blind phase (N=634) or Week 96 of the extension phase (n=1025) *[see Clinical Studies (13.2)]* who had HIV-1 RNA greater than or equal to 200 copies/mL at the time of confirmed virologic failure or early study drug discontinuation. In the final resistance analysis population, no specific amino acid substitutions emerged consistently in the 11 treatment failure subjects with evaluable genotypic resistance data and failed to establish an association with genotypic BIC resistance. There were no treatment-emergent NRTI resistance-associated substitutions detected in the 11 evaluated treatment failure isolates. Phenotypic resistance analyses of failure isolates found fold-changes in drug susceptibility below the biological or clinical cutoffs for BIC, FTC, and TFV, compared to wild-type reference HIV-1.

In Virologically Suppressed Adult Subjects: In 2 switch trials, Trials 1844 and 1878 *[see Clinical Studies (13.3)]*, of virologically suppressed HIV-1 infected subjects (n=572), only one subject with virologic rebound in the resistance analysis population had IN genotypic and phenotypic data, and 2 rebounders had RT genotypic and phenotypic data. No subjects had HIV-1 with treatment-emergent genotypic or phenotypic resistance to BIC, FTC, or TAF.

In Virologically Suppressed Pediatric Subjects: In Trial 1474 [see Clinical Studies (13.4)], two of 50 subjects in cohort 1, were evaluated for the development of resistance through Week 48; no amino acid substitutions known to be associated with resistance to BIC, FTC, or TFV were detected. No subjects in cohort 2 met the criteria for resistance analyses.

Cross-Resistance

Bictegravir: Cross-resistance has been observed among INSTIs. The susceptibility of BIC was tested against 64 clinical isolates expressing known INSTI resistance-associated substitutions listed by IAS-USA (20 with single substitutions and 44 with 2 or more substitutions). Isolates with a single INSTI-resistance substitution including E92Q, T97A, Y143C/R, Q148R, and N155H showed less than 2-fold reduced susceptibility to BIC. All isolates (n=14) with more than 2.5-fold reduced susceptibility to BIC (above the biological cutoff for BIC) contained G140A/C/S and Q148H/R/K substitutions; the majority (64.3%, 9/14) had a complex INSTI resistance pattern with an additional INSTI-resistance substitution L74M, T97A, or E138A/K. Of those evaluated isolates containing G140A/C/S and Q148H/R/K substitutions in the absence of additional INSTI-resistance substitutions, 38.5% (5/13) showed more than 2.5-fold reduction. In addition, site-directed mutant viruses

with G118R (dolutegravir and raltegravir treatment-emergent substitution) and G118R+T97A had 3.4- and 2.8-fold reduced susceptibility to BIC, respectively.

BIC demonstrated equivalent antiviral activity with less than 2-fold reductions in susceptibility against HIV-1 variants expressing substitutions associated with resistance to NNRTIs, NRTIs, and PIs, compared with the wild-type virus.

Emtricitabine: Cross-resistance has been observed among NRTIs. FTC-resistant viruses with an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC.

Tenofovir Alafenamide: Cross-resistance has been observed among NRTIs. Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bictegravir

BIC 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 carcinogenic in a 2-year rat study at doses up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans at the recommended dose of BIKTARVY.

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 (AUC) than in humans at the recommended dose of BIKTARVY.

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (25 times the human systemic exposure at the recommended dose of BIKTARVY) or in rats at doses up to 600 mg per kg per day (30 times the human systemic exposure at the recommended dose of BIKTARVY).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC 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 dose of 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 dose of BIKTARVY.

Tenofovir Alafenamide

Since 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 4 times (rats) those observed in humans following a 300 mg dose of TDF. 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 BIKTARVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times the exposure observed in humans at the recommended dose of BIKTARVY. In rats, the study was negative for carcinogenic findings.

TAF 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 the human dose of BIKTARVY 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.

12.2 Animal Toxicology and/or 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 7 (TAF) and 14 (tenofovir) times the exposure seen in humans with the recommended daily dose of BIKTARVY.

13 CLINICAL STUDIES

13.1 Description of Clinical Trials

The efficacy and safety of BIKTARVY were evaluated in the trials summarized in Table 11.

Table 11 Trials Conducted with BIKTARVY in Subjects with HIV-1 Infection

Trial	Population	Trial Arms (N)	Timepoint (Week)
Trial 1489[a] (NCT 02607930)	Adults with no antiretroviral treatment history	BIKTARVY (314) ABC/DTG/3TC (315)	144 + 96 (OLE)[b]
Trial 1490[a] (NCT 02607956)		BIKTARVY (320) DTG + FTC/TAF(325)	144 + 96 (OLE)[b]
Trial 1844[a] (NCT 02603120)	Virologically-suppressed[d] adults	BIKTARVY (282) ABC/DTG/3TC (281)	48
Trial 1878[c] (NCT 02603107)		BIKTARVY (290) ATV or DRV (with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC (287)	48
Trial 1825[e]	Virologically-suppressed[d] adults with ESRD[f] receiving chronic hemodialysis	FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination (55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY.	48[g]
Trial 4449[e] (NCT 03405935)	Virologically-suppressed[d] adults aged 65 years and over	BIKTARVY (86)	48
Trial 1474[e] (cohort 1) (NCT 02881320)	Virologically-suppressed[d] adolescents between the ages of 12 to less than 18 years (at least 35 kg)	BIKTARVY (50)	48
Trial 1474[e] (cohort 2) (NCT 02881320)	Virologically-suppressed[d] children between the ages of 6 to less than 12 years (at least 25 kg)	BIKTARVY (50)	24

OLE = open-label extension

a. Randomized, double blind, active controlled trial.

b. 144-week double-blind active controlled phase followed by an extension phase in which 1025 subjects from Trials 1489 and 1490 received open-label BIKTARVY for 96 weeks.

c. Randomized, open label, active controlled trial.

d. HIV-1 RNA less than 50 copies per mL.

e. Open label trial.

f. End stage renal disease (estimated creatinine clearance of less than 15 mL per minute by Cockcroft-Gault method).

g. Subjects received FTC+TAF in combination with elvitegravir and cobicistat for 96 weeks, followed by an extension phase in which 10 subjects received BIKTARVY for 48 weeks.

13.2 Clinical Trial Results in HIV-1 Subjects with No Antiretroviral Treatment History

In Trial 1489, subjects were randomized in a 1:1 ratio to receive either BIKTARVY (N=314) or ABC/DTG/3TC (600 mg/50 mg/300 mg) (N=315) once daily. In Trial 1490, subjects were randomized in a 1:1 ratio to receive either BIKTARVY (N=320) or DTG + FTC/TAF (50 mg + 200 mg/25 mg) (N=325) once daily.

In Trial 1489, the mean age was 34 years (range 18–71), 90% were male, 57% were White, 36% were Black, and 3% were Asian. 22% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3–6.5). The mean baseline CD4+ cell count was 464 cells per mm^3 (range 0–1424) and 11% had CD4+ cell counts less than 200 cells per mm^3. 16% of subjects had baseline viral loads greater than 100,000 copies per mL.

In Trial 1490, the mean age was 37 years (range 18–77), 88% were male, 59% were White, 31% were Black, and 3% were Asian. 25% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 2.3–6.6). The mean baseline CD4+ cell count was 456 cells per mm^3 (range 2–1636) and 12% had CD4+ cell counts less than 200 cells per mm^3. 19% of subjects had baseline viral loads greater than 100,000 copies per mL.

In both trials, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies per mL, or greater than 400,000 copies per mL), by CD4 count (less than 50 cells per mm^3, 50-199 cells per mm^3, or greater than or equal to 200 cells per mm^3), and by region (US or ex-US).

Treatment outcomes of Trials 1489 and 1490 through Week 144 are presented in Table 12.

Table 12 Virologic Outcomes of Randomized Treatment in Trials 1489 and 1490 at Week 144[a] in Subjects with No Antiretroviral Treatment History

	Trial 1489		**Trial 1490**	
	BIKTARVY (N=314)	**ABC/DTG/3TC** (N=315)	**BIKTARVY** (N=320)	**DTG + FTC/TAF** (N=325)
HIV-1 RNA < 50 copies/mL	82%	84%	82%	84%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-2.6% (-8.5% to 3. 4%)		-1.9% (-7.8% to 3.90%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	3%	5%	3%
No Virologic Data at Week 144 Window	18%	13%	13%	13%
Discontinued Study Drug Due to AE or Death[c]	1%	2%	3%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	16%	11%	11%	9%
Missing Data During Window but on Study Drug	1%	<1%	0%	1%

a. Week 144 window was between Day 967 and 1050 (inclusive).

b. Includes subjects who had ≥ 50 copies/mL in the Week 144 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Trials 1489 and 1490, the mean increase from baseline in CD4+ count at Week 144 was 299 and 317 cells per mm^3 in the BIKTARVY and ABC/DTG/3TC groups, respectively, and 278 and 289 cells per mm^3 in the BIKTARVY and DTG + FTC/TAF groups, respectively.

13.3 Clinical Trial Results in HIV-1 Virologically-Suppressed Subjects Who Switched to BIKTARVY

In Trial 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY were evaluated in a randomized, double-blind trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=563, randomized and dosed). Subjects must have been stably suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 3 months prior to trial entry and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY at baseline (N=282), or stay on their baseline antiretroviral regimen (N=281). Subjects had a mean age of 45 years (range 20–71), 89% were male, 73% were White, and 22% were Black. 17% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 723 cells per mm^3 (range 124–2444).

In Trial 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (given with either cobicistat or ritonavir) to BIKTARVY were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N=577, randomized and dosed). Subjects must have been stably suppressed on their baseline regimen for at least 6 months, must not have been previously treated with any INSTI, and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY (N=290) or stay on their baseline antiretroviral regimen (N=287). Subjects had a mean age of 46 years (range 20–79), 83% were male, 66% were White, and 26% were Black. 19% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells per mm^3 (range 62–2582). Subjects were stratified by prior treatment regimen. At screening, 15% of subjects were receiving ABC/3TC plus ATV or DRV (given with either cobicistat or ritonavir) and 85% of subjects were receiving FTC/TDF plus ATV or DRV (given with either cobicistat or ritonavir).

Treatment outcomes of Trials 1844 and 1878 through Week 48 are presented in Table 13.

Table 13 Virologic Outcomes of Trials 1844 and 1878 at Week 48[a] in Virologically-Suppressed Subjects who Switched to BIKTARVY

	Trial 1844		**Trial 1878**	
	BIKTARVY (N=282)	**ABC/DTG/3TC** (N=281)	**BIKTARVY** (N=290)	**ATV- or DRV-based regimen[b]** (N=287)
HIV-1 RNA ≥ 50 copies/mL[c]	1%	<1%	2%	2%

	Trial 1844		Trial 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC** (N=281)	**BIKTARVY** (N=290)	**ATV- or DRV-based regimen[b]** (N=287)
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

a. Week 48 window was between Day 295 and 378 (inclusive).
b. ATV given with cobicistat or ritonavir or DRV given with cobicistat or ritonavir plus either FTC/TDF or ABC/3TC.
c. Includes subjects who had ≥ 50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In Trial 1844, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was -31 cells per mm^3 in subjects who switched to BIKTARVY and 4 cells per mm^3 in subjects who stayed on ABC/DTG/3TC.

In Trial 1878, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was 25 cells per mm^3 in patients who switched to BIKTARVY and 0 cells per mm^3 in patients who stayed on their baseline regimen.

In Trial 1825, an open-label single arm trial, the efficacy, safety, and pharmacokinetics of FTC and TAF (components of BIKTARVY) were evaluated in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects [median age (range): 55 years (34 to 63)] switched to BIKTARVY and all subjects remained virologically suppressed (HIV-1 RNA < 50 copies/mL) for 48 weeks.

In Trial 4449, the efficacy and safety of switching from a stable antiretroviral regimen to BIKTARVY were evaluated in an open-label, single arm trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults aged 65 years and over (N=86). Subjects treated with BIKTARVY had a mean age of 70 years (range: 65 to 80). The primary endpoint was the proportion of subjects with HIV RNA > 50 copies/mL at Week 48. No

subjects had HIV RNA > 50 copies/mL. Ninety-one percent (78/86) of subjects remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. Eight subjects did not have virologic data at the Week 48 timepoint due to discontinuation or missing data.

13.4 Clinical Trial Results in HIV-1 Infected Pediatric Subjects Between the Ages of 6 to Less than 18 Years

In Trial 1474, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of BIKTARVY in HIV-1 infected pediatric subjects were evaluated in virologically-suppressed adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50) and in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=50), who were virologically suppressed for ≥ 6 months prior to screening on a stable antiretroviral regimen.

Cohort 1: Virologically-suppressed adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with BIKTARVY once daily had a mean age of 14 years (range: 12 to 17) and a mean baseline weight of 51.7 kg (range: 35 to 123), 64% were female, 27% were Asian and 65% were black. At baseline, median CD4+ cell count was 750 cells per mm^3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%).

After switching to BIKTARVY, 98% (49/50) of subjects in cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells per mm^3.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with BIKTARVY once daily had a mean age of 10 years (range: 6 to 11) and a mean baseline weight of 31.9 kg (range: 25 to 69), 54% were female, 22% were Asian and 72% were black. At baseline, median CD4+ cell count was 898 cells per mm^3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%).

After switching to BIKTARVY, 100% (50/50) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -24 cells per mm^3.

14 HOW SUPPLIED/STORAGE AND HANDLING

BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side.

Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Do not remove the desiccant packet.

Each BIKTARVY tablet contains 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF).

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

15 PATIENT COUNSELING INFORMATION

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of BIKTARVY *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue BIKTARVY without first informing their healthcare provider.

Drug Interactions

BIKTARVY may interact with certain drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort *[see Contraindications (4) and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.3)]*.

Renal Impairment

Advise patients to avoid taking BIKTARVY with concurrent or recent use of nephrotoxic agents. Renal impairment including cases of acute renal failure has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to BIKTARVY. Advise patients that they should stop BIKTARVY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Missed Dosage

Inform patients that it is important to take BIKTARVY on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to BIKTARVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

16. PRODUCT OWNER

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Ireland

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