SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8.

1. NAME OF THE MEDICINAL PRODUCT

Dolutegravir (as sodium)/Lamivudine/Tenofovir disoproxil fumarate 50mg/300mg/300mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg dolutegravir (as sodium), 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate.

Excipients with known effect

Each film-coated tablet contains 145.00 mg of mannitol.

Each film-coated tablet contains 6.44 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue coloured, capsule shaped biconvex film coated tablet, debossed with 'C' on one side and plain on other side.

Dimensions: 20.00 mm x 9.00 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets are indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and paediatric patients weighing at least 40 kg.

Limitations of use:

• Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should not be used in combination with ATRIPLA, COMBIVIR, COMPLERA, EPIVIR, EPIVIR-HBV, EPZICOM, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TIVICAY, TRIUMEQ, TRUVADA, VEMLIDY or VIREAD (see section 4.4).

4.2 Posology and method of administration

Posology

Recommended dose in adults and paediatric patients weighing at least 40 kg

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets may be taken with or without food.

The recommended dose of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablet is one tablet daily in treatment-naïve or treatment-experienced INSTI-naïve and treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (see section 4.5).

Patients with renal impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with renal impairment has not yet been established.

Patients with hepatic impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with hepatic impairment has not yet been established.

Method of administration

Oral use.

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets can be taken with or without food.

4.3 Contraindications

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablet is contraindicated in patients:

• With previous hypersensitivity to dolutegravir, lamivudine or tenofovir disoproxil fumarate or to any of the excipients listed in section 6.1.

• receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir

(as sodium)/lamivudine/tenofovir disoproxil fumarate tablets and other suspect medicinal products immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets or other suspect medicinal products after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablet is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets (see section 4.8). In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

Lamivudine

Posttreatment exacerbations of hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown.

Emergence of lamivudine-resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV (see labeling for EPIVIR-HBV). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in

HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Tenofovir disoproxil fumarate

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets.

Lactic acidosis and severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets 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).

Use with interferon- and ribavirin-based regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients (see section 5.2), hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the labeling for interferon and ribavirin.

Pancreatitis

In paediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine

should be used with caution. Treatment with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

New onset or worsening renal impairment

Tenofovir is principally eliminated by the kidney. 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 disoproxil fumarate (see section 4.8).

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA® (adefovir dipovoxil), it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets, and periodically during dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets therapy.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance below 50 mL/min (see section 4.2). No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) (see section 4.5). Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Coadministration with other medicinal products

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should not be used in combination with other medicinal products containing dolutegravir, lamivudine, tenofovir disoproxil fumarate or tenofovir alafenamide, including ATRIPLA, COMBIVIR, COMPLERA,

EPIVIR, EPIVIR-HBV, EPZICOM, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, TIVICAY, TRIUMEQ, TRUVADA, VEMLIDY or VIREAD. Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should not be administered in combination with HEPSERA (adefovir dipivoxil) (see section 4.5).

Bone effects

Bone mineral density

In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fumarate (see section 4.5).

Clinical trials evaluating tenofovir disoproxil fumarate in paediatric and adolescent subjects were conducted. Under normal circumstances BMD increases rapidly in paediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate-treated HIV-1 infected paediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all paediatric trials, skeletal growth (height) appeared to be unaffected (see section 4.5).

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and paediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate (see section 4.8). Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving medicinal products containing tenofovir disoproxil fumarate.

Fat redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir, lamivudine and tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond 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, and Guillain-Barré syndrome) 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.

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

The concomitant use of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablet and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

• Loss of therapeutic effect of dolutegravir and possible development of resistance.

• Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 6 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 therapy with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets; review concomitant medications during therapy with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets; and monitor for the adverse reactions associated with the concomitant drugs.

Mannitol

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablet contains mannitol. Patients may have a mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of dolutegravir on the pharmacokinetics of other medicinal products

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC50 = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 microM). *In vivo*,

dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 1) (see section 4.3).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC50 = 2.12 microM) and OAT3 (IC50 = 1.97 microM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC50 greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

Effect of other medicinal products on the pharmacokinetics of dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir /ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 1) (see section 5.2).

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Established and other potentially significant drug interactions

Table 1 provides clinical recommendations as a result of drug interactions with dolutegravir. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy (see sections 4.2 and 5.2).

Table 1. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions (see section 4.2)

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir and/or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral medicinal products		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of dolutegravir with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In paediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b.]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavira Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg

		twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In paediatric patients, increase the weight-based dose to twice daily. Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance
Other medicinal products		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with dolutegravir *[see Contraindications (4)]*.
Carbamazepine[a]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In paediatric patients, increase the weight-based dose to twice daily. Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
	↓Dolutegravir	

Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)		Avoid coadministration with dolutegravir because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacidsa or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer dolutegravir 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir. When stopping dolutegravir, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dose of dolutegravir to 50 mg twice daily for treatment-naïve and treatment-

		experienced, INSTI-naïve adult patients. In paediatric patients, increase the weight-based dose to twice daily. Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b]

See section 5.2 Table 33 or Table 34 for magnitude of interaction.

b The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance (see section 5.1)) upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to dolutegravir or other coadministered antiretroviral medicinal products.

Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

Drugs inhibiting organic cation transporters

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) (see section 5.2). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Didanosine

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with tenofovir disoproxil fumarate, Cmax and AUC of didanosine increased significantly (see section 5.2). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with tenofovir disoproxil fumarate. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with tenofovir disoproxil fumarate. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional information on coadministration of tenofovir disoproxil fumarate and didanosine, please refer to the full prescribing information for didanosine.

HIV-1 protease inhibitors

Tenofovir disoproxil fumarate decreases the AUC and Cmin of atazanavir (see section 5.2). When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations (see section 5.2). Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavir boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Hepatitis C antiviral medicinal products

Coadministration of tenofovir disoproxil fumarate and EPCLUSA® (sofosbuvir/velpatasvir) or HARVONI® (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure (see section 5.2).

In patients receiving tenofovir disoproxil fumarate concomitantly with EPCLUSA, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving tenofovir disoproxil fumarate concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

Drugs affecting renal function

Since tenofovir is primarily eliminated by the kidneys (see section 5.2), coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see section 4.4).

In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets should be used during pregnancy only if clearly needed.

Breast-feeding

It is recommended that HIV-1-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV. It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown.

Fertility

Limited human data on the effect of dolutegravir and tenofovir disoproxil fumarate on fertility are available. In animals, there was no harmful effects on fertility with dolutegravir, lamivudine or tenofovir disoproxil fumarate (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness may occur during treatment with dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets.

4.8 Undesirable effects

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials experience in adult subjects

Dolutegravir

Treatment-naïve subjects: The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 2. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 2. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis

	SPRING-2		**SINGLE**	
System Organ Class/ Preferred Term	**Dolutegravir**	**Raltegravir 400 mg Twice**	**Dolutegravir**	**ATRIPLA Once Daily (n = 419)**

	50 mg Once Daily + 2 NRTIs (n = 403)	Daily + 2 NRTIs (n = 405)	50 mg + EPZICOM Once Daily (n = 414)	
Psychiatric Insomnia Depression Abnormal dreams	<1% <1% <1%	<1% <1% <1%	3% 1% <1%	3% 2% 2%
Nervous System Dizziness Headache	<1% <1%	<1% <1%	<1% 2%	5% 2%
Gastrointestinal Nausea Diarrhea	1% <1%	1% <1%	<1% <1%	3% 2%
Skin and Subcutaneous Tissue Rasha	0	<1%	<1%	6%
General Disorders Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth Vertigo	0	<1%	0	2%

Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and ATRIPLA, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received dolutegravir 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either EPZICOM or TRUVADA). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir and 6% in subjects receiving darunavir/ritonavir. The ARs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent AR of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-experienced, integrase strand transfer inhibitor-experienced subjects: In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent ARs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials.

Less common adverse reactions observed in treatment-naïve and treatment-experienced trials: The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary disorders: Hepatitis.

Musculoskeletal disorders: Myositis.

Psychiatric disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and urinary disorders: Renal impairment.

Skin and subcutaneous tissue disorders: Pruritus.

Laboratory abnormalities

Treatment-naïve subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING -2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419
ALT Grade 2 (>2.5-5.0 x ULN) Grade 3 to 4 (>5.0 x ULN)	 4% 2%	 4% 2%	 3% 1%	 5% <1%
AST Grade 2 (>2.5-5.0 x ULN) Grade 3 to 4 (>5.0 x ULN)	 5% 3%	 3% 2%	 3% 1%	 4% 3%
Total Bilirubin Grade 2 (1.6-2.5 x ULN) Grade 3 to 4 (>2.5 x ULN)	3% <1%	2% <1%	<1% <1%	<1% <1%
Creatine kinase Grade 2 (6.0-9.9 x ULN) Grade 3 to 4 (≥10.0 x ULN)	2% 7%	5% 4%	5% 7%	3% 8%
Hyperglycemia				

Grade 2 (126-250 mg/dL) Grade 3 (>250 mg/dL)	6% <1%	6% 2%	9% 2%	6% <1%
Lipase Grade 2 (>1.5-3.0 x ULN) Grade 3 to 4 (>3.0 x ULN	7% 2%	7% 5%	11% 5%	11% 4%
Total neutrophils Grade 2 (0.75-0.99 x 109) Grade 3 to 4 (<0.75 x 109)	4% 2%	3% 2%	4% 3%	5% 3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysisa) and SINGLE Trials (Week 144 Analysisa)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: dolutegravir + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: dolutegravir n = 9, raltegravir n = 13; SINGLE: dolutegravir + EPZICOM n = 36 and ATRIPLA: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials

Treatment-experienced, integrase strand transfer inhibitor-experienced subjects: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of subjects had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported

Hepatitis B and/or hepatitis C virus co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn (see section 4.4).

Changes in serum creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (see section 5.1). Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Lamivudine

The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1-infected subjects in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea, and cough.

Selected clinical adverse reactions in greater than or equal to 5% of subjects during therapy with lamivudine 150 mg twice daily plus RETROVIR 200 mg 3 times daily for up to 24 weeks are listed in Table 5.

Table 5. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	Lamivudine 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR[a] (n = 230)
Body as a Whole Headache Malaise & fatigue Fever or chills	35% 27% 10%	27% 23% 12%
Digestive Nausea Diarrhea Nausea & vomiting Anorexia and/or decreased appetite Abdominal pain Abdominal cramps Dyspepsia	33% 18% 13% 10% 9% 6% 5%	29% 22% 12% 7% 11% 3% 5%
Nervous system Neuropathy Insomnia & other sleep disorders Dizziness Depressive disorders	12% 11% 10% 9%	10% 7% 4% 4%
Respiratory Nasal signs & symptoms Cough	20% 18%	11% 13%
Skin Skin rashes	9%	6%
Musculoskeletal Musculoskeletal pain Myalgia Arthralgia	12% 8% 5%	10% 6% 5%

Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis: Pancreatitis was observed in 9 out of 2,613 adult subjects (0.3%) who received lamivudine in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007 (see section 4.4).

Lamivudine 300 mg once daily: The types and frequencies of clinical adverse reactions reported in subjects receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 6.

Table 6. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Trial (NUCB3007

	24-Week Surrogate Endpoint Trialsa		Clinical Endpoint Triala	
Test (Threshold Level)	Lamivudine plus RETROVIR	RETROVIR[b]	Lamivudine plus Current Therapyc[c]	Placebo plus Current Therapyc[c]
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 × ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 × ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 × ULN);	0.8%	0.4%	ND	ND
Amylase (>2.0 × ULN)	4.2%	1.5%	2.2%	1.1%

a The median duration on study was 12 months.

b Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

c Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in subjects receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Tenofovir disoproxil fumarate

More than 12,000 subjects have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access programs. A total of 1544 subjects have received tenofovir

disoproxil fumarate 300 mg once daily in clinical trials; over 11,000 subjects have received tenofovir disoproxil fumarate in expanded access programs.

The most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Treatment-naïve patients

Study 903 - treatment-emergent adverse-reactions: The most common adverse reactions seen in a double-blind comparative controlled trial in which 600 treatment-naïve subjects received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 7.

Table 7: Selected Treatment-Emergent Adverse Reactions[a] (Grades 2-4) Reported in ≥5% in Any Treatment Group in Study 903 (0-144 Weeks)

	Tenofovir disoproxil fumarate + 3TC+EFV	d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal Pain	7%	12%
Back Pain	9%	8%
Asthenia	6%	75
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic disorders		
Lipodystrophy[b]	1%	7%
Musculoskeletal		
Arthralgia	5%	7%
Myalagia	3%	5%
Nervous System		
Depression	11%	10%

Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[c]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[d]	18%	12%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

c. Peripheral neuropathy includes peripheral neuritis and neuropathy.

d. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%), respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grades 3 - 4 laboratory abnormalities is provided in Table 8.

Table 8: Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil fumarate-Treated Subjects in Study 903 (0-144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	Tenofovir disoproxil fumarate + 3TC + EFV
	N=299	N=301
Any ≥Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%

Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - treatment emergent adverse reactions: In Study 934,511 antiretroviral-naïve subjects received either tenofovir disoproxil fumarate + EMTRIVA® administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve subjects (Table 9).

Changes in bone mineral density

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate+ lamivudine + efavirenz (−2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (−1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (−2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. −2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate -treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range (see section 4.4).

Table 9: Selected Treatment-Emergent Adverse Reactionsa (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0-144 Weeks)

	Tenofovir disoproxil fumarate[b] + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder Diarrhea Nausea Vomiting	9% 9% 2%	5% 7% 5%
General Disorders and Administration Site Condition Fatigue	9%	8%
Infections and Infestations	8%	4%

Sinusitis Upper respiratory tract infections Nasopharyngitis	8% 5%	5% 3%
Nervous System Disorders Headache Dizziness	6% 8%	5% 7%
Psychiatric Disorders Depression Insomnia	9% 5%	7% 7%
Skin and Subcutaneous Tissue Disorders Rash event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

Laboratory abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in previous trials (Table 10).

Table 10: Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	Tenofovir disoproxil fumaratea + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L; F: >170 U/L)	3%	3%

ALT (M: >215 U/L; F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of Tenofovir disoproxil fumarate + EMTRIVA with efavirenz.

Treatment-experienced patients

Treatment-emergent adverse reactions: The adverse reactions seen in treatment-experienced subjects were generally consistent with those seen in treatment-naïve subjects including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of subjects discontinued participation in the clinical trials due to gastrointestinal adverse reactions (Study 907).

A summary of moderate to severe treatment-emergent adverse reactions that occurred during the first 48 weeks of Study 907 is provided in Table 11.

Table 11. Selected Treatment-Emergent Adverse Reactionsa (Grades 2-4) Reported in ≥3% in Any Treatment Group in Study 907 (0-48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0-24)	Placebo (N=182) (Week 0-24)	Tenofovir disoproxil fumarate (N=368) (Week 0-48)	Placebo crossover to Tenofovir disoproxil fumarate (N=170) (Week 24-48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	12%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%

Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy[b]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event[c]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. Peripheral neuropathy includes peripheral neuritis and neuropathy.

c. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory abnormalities: Laboratory abnormalities observed in this trial occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grades 3-4 laboratory abnormalities is provided in Table 12.

Table 12. Grades 3-4 Laboratory Abnormalities Reported in ≥1% of Tenofovir disoproxil fumarate-Treated Subjects in Study 907 (0–48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0-24)	Placebo (N=182) (Week 0–24)	Tenofovir disoproxil fumarate (N=368) (Week 0-48)	Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24-48)

Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glucosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750 mm3)	1%	1%	2%	1%

Clinical trials experience in paediatric subjects

Dolutegravir

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected paediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled (see section 5.1).

The adverse reaction profile was similar to that for adults. Grade 2 ARs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ARs reported. No ARs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

Lamivudine

Lamivudine oral solution has been studied in 638 paediatric subjects aged 3 months to 18 years in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a greater than or equal to 5% frequency during therapy with lamivudine 4 mg per kg twice daily plus RETROVIR 160 mg per m2 3 times daily in therapy-naive (less than or equal to 56 days of antiretroviral therapy) paediatric subjects are listed in Table 13.

Table 13. Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal to 5% Frequency) in Paediatric Subjects in Trial ACTG300

Adverse Reaction	Lamivudine plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a Whole Fever	25%	32%
Digestive Hepatomegaly Nausea & vomiting Diarrhea Stomatitis Splenomegaly	11% 8% 8% 6% 5%	11% 7% 6% 12% 8%
Respiratory Cough Abnormal breath sounds/wheezing	15% 7%	18% 9%
Ear, Nose, and Throat Signs or symptoms of earsa Nasal discharge or congestion	7% 8%	6% 11%
Other Skin rashes Lymphadenopathy	12% 9%	14% 11%

Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced paediatric subjects receiving lamivudine alone or in combination with other antiretroviral medicinal products. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to lamivudine plus RETROVIR. Pancreatitis was

observed in 1 subject in this trial who received open-label lamivudine in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy (see section 4.4).

Paresthesias and peripheral neuropathies: Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in Trial NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (less than or equal to 56 days of antiretroviral therapy) paediatric subjects are listed in Table 14.

Table 14. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Paediatric Subjects in Trial ACTG300

Test (Threshold Level)	Lamivudine plus RETROVIR	Didanosine
Absolute neutrophil count (<400/mm3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total Amylase (>2.5 × ULN)	3%	3%

ULN = Upper limit of normal.

Tenofovir disoproxil fumarate

Assessment of adverse reactions is based on two randomized trials (Studies 352 and 321) in 184 HIV-1 infected paediatric subjects (2 to less than 18 years of age) who received treatment with tenofovir disoproxil fumarate (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral medicinal products for 48 weeks. The adverse reactions observed in subjects who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials in adults.

Eighty-nine paediatric subjects (2 to less than 12 years of age) received tenofovir disoproxil fumarate in Study 352 for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score (see section 4.4).

Changes in bone mineral density

Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil

fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were −0.341 for lumbar spine and −0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment groups. One tenofovir disoproxil fumarate-treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z scores were −0.012 for lumbar spine and −0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected (see section 4.4).

Post marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions 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.

Dolutegravir

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety.

Lamivudine

Body as a Whole

Redistribution/accumulation of body fat (see section 4.4).

Endocrine and Metabolic

Hyperglycemia.

General

Weakness. Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis (see section 4.4), post treatment exacerbations of hepatitis B (see section 4.4).

Hypersensitivity

Anaphylaxis, urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Skin

Alopecia, pruritus.

Tenofovir disoproxil fumarate

Immune System Disorders

Allergic reaction, including angioedema

Metabolism and Nutrition Disorders

Lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders

Rash

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions

Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia

Hemic and Lymphatic

Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis (see section 4.4), post treatment exacerbations of hepatitis B (see

Section 4.4).

Hypersensitivity

Anaphylaxis, urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Skin

Alopecia, pruritus.

<u>Tenofovir disoproxil fumarate</u>

Immune System Disorders

Allergic reaction, including angioedema

Metabolism and Nutrition Disorders

Lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders

Rash

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy,interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions

Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

There is no known specific treatment for overdose with dolutegravir or lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations ATC code: J05AR12.

Dolutegravir, lamivudine and tenofovir disoproxil fumarate are HIV-1 antiviral agent.

Effects on electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50- mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QT^C change based on Fridericia correction method

(QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours' post-dose.

Effects on renal function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) nor did effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compare with the placebo.

Mechanism of action

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Lamivudine

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5´-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine Monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral activity

Dolutegravir

Antiviral activity in cell culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC50 values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC50 value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC50 values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC50 values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral activity in combination with other antiviral medicinal products

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the

fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Lamivudine

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC50 value were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC50 values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM),20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC50 values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Tenofovir disoproxil fumarate

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 (50% effective concentration) values for tenofovir were in the range of 0.04 µM to 8.5 µM.

In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir,ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D,

E, F, G, and O (EC50 values ranged from 0.5 µM to 2.2 µM) and strain-specific activity against HIV-2 (EC50 values ranged from 1.6 µM to 5.5 µM).

Resistance

Dolutegravir

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-naïve subjects: No subjects in the dolutegravir 50-mg once-daily treatment arms of treatmentnaïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data.

In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and

G163K/R) and raltegravir phenotypic resistance.

Treatment-experienced, integrase strand transfer inhibitor-experienced subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen. Use of dolutegravir in INSTI-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of dolutegravir 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

<u>Lamivudine</u>

Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either valine or isoleucine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

Tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2- to 4- fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) of analyzed patient isolates in the tenofovir disoproxil fumarate arm and in 2/49 (4%) of analyzed patient isolates in the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 occurred in the first 48 weeks of treatment and one at Week 96. Other patient in the tenofovir disoproxil fumarate arm developed the K70E substitution in the virus.

Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this trial.

In Study 934 of treatment-naïve subjects (tenofovir disoproxil fumarate + EMTRIVA + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation showed development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the two treatment arms. The M184V substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 of analyzed subject isolates in the tenofovir disoproxil fumarate + EMTRIVA group and in 10/29 of analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Response by baseline genotype

Dolutegravir

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K,

and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis at Week 48 (n = 175)

(Table 15). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 15). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 15. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase

Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Week 48 (<50 copies/mL) n = 175
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions[bc]	29% (6/21)

a Includes INSTI-resistance substitutions Y143R/C/H and N155H.

b INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).

c The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions

Response by baseline phenotype

Dolutegravir

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 16). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide

clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 16. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subject with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3-<10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase strand transfer inhibitor treatment-emergent resistance

Dolutegravir

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1

RNA greater than 400 copies per mL at the failure time point, Week 48 or beyond, or the last time point on trial.

Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) subjects in the Week 48 resistance analysis.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Genotypic and phenotypic analysis of on-therapy HIV-1 isolates from subjects with virologic failure

Lamivudine

Trial EPV20001: Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level greater than or equal to 400 copies per mL) by Week 48. Twenty-eight subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 log10 copies per mL and 4.6 log10 copies per mL, respectively.

Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed that isolates from 8 of 22 subjects contained a treatment-emergent lamivudine resistance-associated substitution (M184V or M184I), isolates from 0 of 22 subjects contained treatment emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W,T215Y/F, or K219Q/E), and isolates from 10 of 22 subjects contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C).

Genotypic analysis of on-therapy isolates from subjects (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 5 of 22 subjects contained treatment-emergent lamivudine resistance substitutions, isolates from 1 of 22 subjects contained treatment-emergent zidovudine resistance substitutions, and isolates from 7 of 22 subjects contained treatment-emergent efavirenz resistance substitutions.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine once daily showed that isolates from 7 of 13 subjects showed an 85- to 299-fold decrease in susceptibility to lamivudine, isolates from 12 of 13 subjects were susceptible to zidovudine, and isolates from 8 of 13 subjects exhibited a 25- to 295-fold decrease in susceptibility to efavirenz.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine twice daily showed that isolates from 4 of 13 subjects exhibited a 29- to 159-fold decrease in susceptibility to lamivudine, isolates from all 13 subjects were susceptible to zidovudine, and isolates from 3 of 13 subjects exhibited a 21- to 342-fold decrease in susceptibility to efavirenz.

Trial EPV40001: Fifty subjects received lamivudine 300 mg once daily plus zidovudine 300 mg twice daily plus abacavir 300 mg twice daily and 50 subjects received lamivudine 150 mg plus zidovudine 300 mg plus abacavir 300 mg all twice-daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 log10 copies per mL and 4.83 log10 copies per mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone, and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from subjects (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 subjects exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 subjects were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from subjects (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 subject exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

Paediatrics: Paediatric subjects receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions (abacavir, nevirapine/efavirenz, or zidovudine) in ARROW developed viral resistance more frequently than those receiving tablets. At randomization to once-daily or twice-daily dosing of lamivudine plus abacavir, 13% of subjects who started on tablets and 32% of subjects who started on solution had resistance substitutions. The resistance profile observed in paediatrics is similar to that observed in adults in terms of the genotypic substitutions detected and relative frequency, with the most commonly detected substitutions at M184 (V or I).

Cross-resistance

Dolutegravir

Site-directed integrase strand transfer inhibitor-resistant mutant HIV-1 and HIV-2 strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses.

The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range:2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse transcriptase inhibitor- and protease inhibitor-resistant strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

Lamivudine

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Lamivudineresistant HIV-1 mutants were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir disoproxil fumarate

Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors the K65R or K70E substitution. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of three zidovudine-associated reverse transcriptase substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced subjects (tenofovir disoproxil fumarate + Standard Background Therapy (SBT) compared to placebo + SBT), 14/304 (5%) of the tenofovir disoproxil fumarate-treated subjects with virologic failure through Week 96 had greater than 1.4-fold (median 2.7- fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R substitution in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment-experienced subjects participating in Studies 902 and 907. In these clinical trials, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI substitution. Virologic responses for subjects in the genotype substudy were similar to the overall trial results.

Several exploratory analyses were conducted to evaluate the effect of specific substitutions and substitutional patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross resistance of tenofovir disoproxil fumarate to pre-existing zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) were observed and appeared to depend on the type and number of specific substitutions. Tenofovir disoproxil fumarate-treated subjects whose HIV-1 expressed 3 or more zidovudine resistance-associated substitutions that included either the M41L or L210W reverse transcriptase substitution showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still

improved compared with placebo. The presence of the D67N, K70R, T215Y/F, or K219Q/E/N substitution did not appear to affect responses to tenofovir disoproxil fumarate therapy. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to tenofovir disoproxil fumarate. Limited data are available for subjects whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in subjects with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V substitution. HIV-1 RNA responses among these subjects were durable through Week 48. Studies 902 and 907 phenotypic analyses Phenotypic analysis of baseline HIV-1 from treatment-experienced subjects (N=100) demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 17 summarizes the HIV-1 RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 17. HIV-1 RNA Response at Week 24 by Baseline Tenofovir disoproxil fumarate Susceptibility

(Intent-To-Treat)[a]

Baseline Tenofovir disoproxil fumarate Susceptibility[b]	Change in HIV-1 RNA[c] (N)
<1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
>4	-0.12 (9)

a. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).

b. Fold change in susceptibility from wild-type.

c. Average HIV-1 RNA change from baseline through Week 24 (DAVG24) in log10 copies/mL.

Clinical studies

Dolutegravir

The efficacy and safety of dolutegravir were evaluated in the studies summarized in Table 18.

Table 18. Trials Conducted with Dolutegravir in HIV-1-Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)

Adults: Treatment-naïve	SPRING-2 (ING113086) (NCT01227824)	Dolutegravir + 2 NRTIs (n = 403) Raltegravir +3 NRTIs (n = 405)	96
	SINGLE (ING114467) (NCT01263015)	Dolutegravir + EPZICOM (n = 414) ATRIPLA (n = 419)	144
	FLAMINGO (ING114915) (NCT01449929)	Dolutegravir + NRTI BR (n = 243) Darunavir/ritonavir + NRTI BR (n = 242)	96
Treatment experienced, INSTI-naïve	SAILING (ING111762) (NCT01231516)	Dolutegravir + BR (n = 354) Raltegravir + BR (n = 361)	48
INSTI-experienced	VIKING-3 (ING112574) (NCT01328041)	Dolutegravir + OBT (n = 183)	48
Pediatrics: 6 years and older without INSTI resistance	IMPAACT P1093 (NCT01302847)	Dolutegravir + BR (n = 46)	48

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy

Lamivudine

The use of lamivudine is based on the results of clinical trials in HIV-1-infected subjects in combination regimens with other antiretroviral medicinal products. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

Adult subjects

Dolutegravir

Treatment-naïve subjects

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline,

the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 19. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 19. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

Lamivudine

The use of lamivudine is based on the results of clinical trials in HIV-1-infected subjects in combination regimens with other antiretroviral medicinal products. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

Adult subjects

Dolutegravir

Treatment-naïve subjects

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose

efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 19. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 19. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2 Week 96		SINGLE Week 144	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZICOM Once Daily (n = 414	ATRIPLA Once Daily (n = 419)
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[d]		8.3% (95% CI: 2.0%, 14.6%)[e]	
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL Discontinued for lack of efficacy Discontinued for other reasons while not suppressed Change in ART regimen	1% 2% <1% <1%	3% 3% 3% <1%	4% 3% 3% 0	<1% 3% 4% 0
No virologic data Reasons Discontinued study/study drug due to adverse event or death[b]	12% 2% 8%	12% 2% 9%	18% 4% 12%	30% 14% 13%

Discontinued study/study drug for other reason[s] Missing data during window but on study	2%	<1%	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
Plasma viral load (copies/mL) ≤100,000 >100,000	84% 79%	83% 63%	73% 69%	64% 61%
Gender Male Female	84% 70%	79% 68%	72% 69%	66% 48%
Race White African-American/African Heritage/Other	83% 77%	78% 75%	72% 71%	71% 47%

a Adjusted for pre-specified stratification factors.

b Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

d The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).

e The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving dolutegravir and 264 cells per mm^3 for the raltegravir group at 96 weeks.

There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving dolutegravir + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm3 (15.6 cells per mm^3, 78.2 cells per mm3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

There was no treatment-emergent resistance to dolutegravir, abacavir, or lamivudine.

FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine [EPZICOM] or fixed-dose emtricitabine/tenofovir disoproxil fumarate [TRUVADA]). There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV-1 RNA greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups. Overall response rates by Snapshot algorithm through Week 96 were 80% for dolutegravir and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving dolutegravir and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with dolutegravir and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-experienced, integrase strand transfer inhibitor-naïve subjects

In the international, multicenter, double-blind trial (SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 20.

Table 20. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg Once Daily + BR[a]	Raltegravir 400 mg Twice Daily + BR[a]

	(n = 354)	(n = 361)
HIV-1 RNA <50 copies/mL	71%	64%
Adjustedb treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data Reasons Discontinued study/study drug due to adverse event or death Discontinued study/study drug for other reasons[c] Missing data during window but on study	9% 3% 5% 2%	9% 4% 4% 1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL) ≤50,000 copies/mL >50,000 copies/mL	 75% 62%	 71% 47%
Background regimen No darunavir use Darunavir use with primary PI substitutions Darunavir use without primary PI substitutions	 67% 85% 69%	 60% 67% 70%
Gender Male Female	70% 74%	66% 60%
Race White African-American/African Heritage/Other	75% 67%	71% 57%

a BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.

b Adjusted for pre-specified stratification factors.

c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm^3 in the group receiving dolutegravir and 153 cells per mm^3 in the raltegravir group.

Treatment-experienced, integrase strand transfer inhibitor-experienced subjects

VIKING-3 examined the effect of dolutegravir 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy (OBT) with continued treatment of dolutegravir 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days, then received dolutegravir with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was 140 cells per mm^3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 log10 (95% CI: 1.3 log10, 1.5 log10). Response at Week 48 was affected by baseline INSTI substitutions.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 21.

Table 21. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg Once Daily + BRa (n = 354)	Raltegravir 400 mg Twice Daily + BRa (n = 361)
HIV-1 RNA <50 copies/mL	71%	64%
Adjustedb treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3% 5%	4% 4%
Discontinued study/study drug for other reasons[c]	2%	1%

Missing data during window but on study		
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL) ≤50,000 copies/mL >50,000 copies/mL	 75% 62%	 71% 47%
Background regimen No darunavir use Darunavir use with primary PI substitutions Darunavir use without primary PI substitutions	67% 85% 69%	60% 67% 70%
Gender Male Female	70% 74%	66% 60%
Race White African-American/African Heritage/Other	 75% 67%	 71% 57%

BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.

b Adjusted for pre-specified stratification factors.

c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm3 in the group receiving dolutegravir and 153 cells per mm3 in the raltegravir group.

Treatment-experienced, integrase strand transfer inhibitor-experienced subjects

VIKING-3 examined the effect of dolutegravir 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy (OBT) with continued treatment of dolutegravir 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days, then received dolutegravir with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects

with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was 140 cells per mm3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 log10 (95% CI: 1.3 log10, 1.5 log10). Response at Week 48 was affected by baseline INSTI substitutions.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 21.

Table 21. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	Dolutegravir 50 mg Twice Daily + OBT (n = 183)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data Reasons Discontinued study/study drug due to adverse event or death	 3%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category	
Gender Male Female	63% 64%
Race White African-American/African Heritage/Other	63% 64%

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 48 in a stepwise fashion.

The median change in CD4+ cell count from baseline was 80 cells per mm3 at Week 48.

Lamivudine

Clinical endpoint trial

NUCB3007 (CAESAR) was a multicenter, double-blind, placebo-controlled trial comparing continued current therapy (zidovudine alone [62% of subjects] or zidovudine with didanosine or zalcitabine [38% of subjects]) to the addition of lamivudine or lamivudine plus an investigational

non-nucleoside reverse transcriptase inhibitor (NNRTI), randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 CD4+ cells per mm^3 (median = 122 cells per mm^3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on trial was 12 months. Results are summarized in Table 22.

Table 22. Number of Subjects (%) with at Least One HIV-1 Disease Progression Event or Death

Endpoint	Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 896)	Lamivudine plus an NNRTI[a] plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

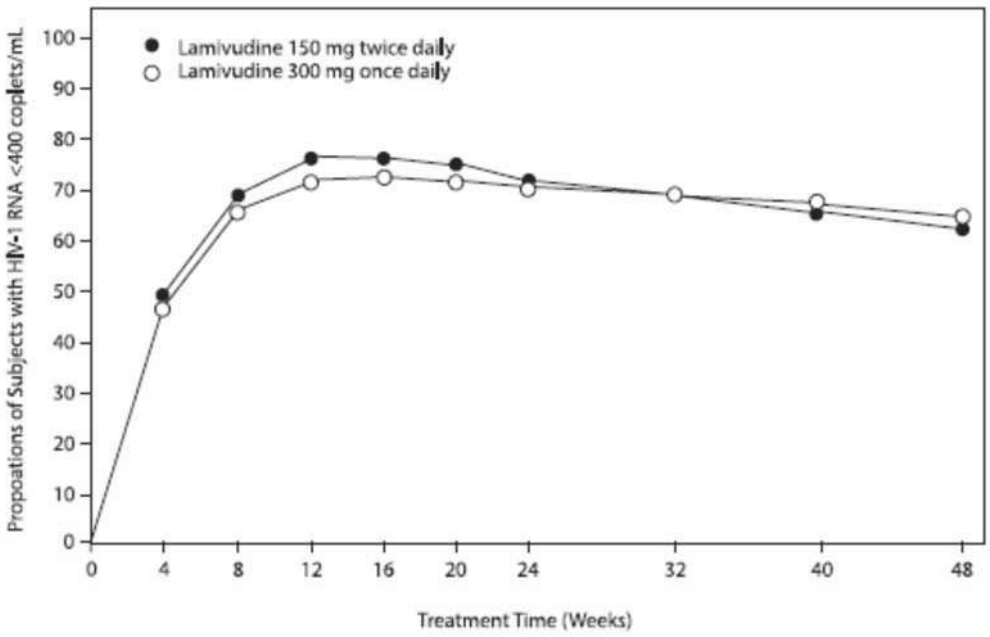
a An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Surrogate endpoint trials

Dual Nucleoside Analogue Trials: Principal clinical trials in the initial development of lamivudine compared lamivudine/zidovudine combinations with zidovudine monotherapy or with zidovudine plus zalcitabine. These trials demonstrated the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in treatment of HIV-1 infection incorporate it into multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

Dose Regimen Comparison Surrogate Endpoint Trials in Therapy-naive Adults: EPV20001 was a multicenter, double-blind, controlled trial in which subjects were randomized 1:1 to receive lamivudine 300 mg once daily or lamivudine 150 mg twice daily, in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naive HIV-1-infected adults enrolled: male (79%), white (50%), median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells per mm3 (median = 362 cells per mm3), and median baseline plasma HIV-1 RNA of 4.66 log10 copies per mL. Outcomes of treatment through 48 weeks are summarized in Figure 1 and Table 23

Figure 1. Virologic Response through Week 48, EPV20001ab (Intent-to-Treat)



a Roche AMPLICOR HIV-1 MONITOR.

b Responders at each visit are subjects who had achieved and maintained HIV-1 RNA less than 400 copies per mL without discontinuation by that visit.

Table 23. Outcomes of Randomized Treatment through 48 Weeks (Intent-to-Treat)

Outcome	Lamivudine 300 mg Once Daily plus RETROVIR plus Efavirenz (n = 278)	Lamivudine 150 mg Twice Daily plus RETROVIR plus Efavirenz (n = 276)
Responder[a]	67%	65%
Virologic failure[b]	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons[s]	18%	14%

a Achieved confirmed plasma HIV-1 RNA less than 400 copies per mL and maintained through 48 weeks.

b Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through Week 48.

c Includes consent withdrawn, lost to follow-up, protocol violation, data outside the trial-defined schedule, and randomized but never initiated treatment.

The proportions of subjects with HIV-1 RNA less than 50 copies per mL (via Roche Ultrasensitive assay) through Week 48 were 61% for subjects receiving lamivudine 300 mg once daily and 63% for subjects receiving lamivudine 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells per mm3 at Week 48 in subjects receiving lamivudine 300 mg once daily and 146 cells per mm3 for subjects receiving lamivudine 150 mg twice daily.

A small, randomized, open-label pilot trial, EPV40001, was conducted in Thailand. A total of 159 treatment-naive adult subjects (male 32%, Asian 100%, median age 30 years, baseline median CD4+ cell count 380 cells per mm^3, median plasma HIV-1 RNA 4.8 log10 copies per mL) were enrolled. Two of the treatment arms in this trial provided a comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of subjects with HIV-1 RNA below 400 copies per mL were 61% (33 of 54) in the group randomized to once-daily lamivudine and 75% (39 of 52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies per mL were 54% (29 of 54) in the once-daily lamivudine group and 67% (35 of 52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells per mm^3 in the once-daily lamivudine group and 216 cells per mm3 in the all-twice-daily group.

Tenofovir disoproxil fumarate

Treatment-naïve adult patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter trial comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4+ cell counts <200 cells/mm3. Treatment outcomes through 48 and 144 weeks are presented in Table 24.

Table 24. Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

	At Week 48	At Week 144

Outcomes	Tenofovir disoproxil fumarate +3TC +EFV (N=299)	d4T+3TC +EFV (N=301)	Tenofovir disoproxil fumarate +3TC +EFV (N=299)	d4T+3TC +EFV (N=301)
Responder[a]	79%	82%	68%	62%
Virologic failure[b]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reason[C]	8%	7%	14%	15%

a. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.

b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mm3). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir disoproxil fumarate and stavudine arms, respectively, achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm3 for the tenofovir disoproxil fumarate arm and 283 cells/mm3 for the stavudine arm.

Through 144 weeks, 11 subjects in the tenofovir disoproxil fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + tenofovir disoproxil fumarate administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects.

From Weeks 96 to 144 of the trial, subjects received a fixed-dose combination of emtricitabine and tenofovir DF with efavirenz in place of emtricitabine + tenofovir disoproxil fumarate with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian, and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log10 copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm3); 41% had CD4+ cell counts <200 cells/mm3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 25.

Table 25. Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC +Tenofovir disoproxil fumarate +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC +Tenofovir disoproxil fumarate +EFV (N=227)[a]	AZT/3TC +EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[c]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue the trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir disoproxil fumarate group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir disoproxil fumarate group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4+ cell count was 190 cells/mm3 in the EMTRIVA + tenofovir disoproxil fumarate group and 158 cells/mm3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm3 at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir disoproxil fumarate group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Treatment-experienced adult patients

Study 907

Study 907 was a 24-week, double-blind placebo-controlled multicenter trial of tenofovir disoproxil fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced subjects. After 24 weeks of blinded trial treatment, all subjects continuing on trial were offered open-label tenofovir disoproxil fumarate for an additional 24 weeks. Subjects had a mean baseline CD4+ cell count of 427 cells/mm3 (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the subjects was 42 years; 85% were male, 69% Caucasian, 17% Black, and 12% Hispanic.

The percent of subjects with HIV-1 RNA <400 copies/mL and outcomes of subjects through 48 weeks are summarized in Table 26.

Table 26. Outcomes of Randomized Treatment (Study 907)

Outcomes	0–24 weeks		0–48 weeks	24–48 weeks
	Tenofovir disoproxil fumarate (N=368)	Placebo (N=182)	Tenofovir disoproxil fumarate (N=368)	Placebo Crossover to Tenofovir disoproxil fumarate (N=170)
HIV-1 RNA <400 copies/mL[a]	40%	11%	28%	30%
Virologic failure[b]	53%	84%	61%	64%

Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[c]	3%	3%	5%	1%

a. Subjects with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.

b. Subjects with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.

c. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of subjects in the tenofovir disoproxil fumarate arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4+ cell counts by Week 24 was +11 cells/mm^3 for the tenofovir disoproxil fumarate group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4+ cell counts by Week 48 was +4 cells/mm3 for the tenofovir disoproxil fumarate group.

Through Week 24, one subject in the tenofovir disoproxil fumarate group and no subjects in the placebo arm experienced a new CDC Class C event.

Paediatric subjects

Dolutegravir

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of dolutegravir in combination treatment regimens in HIV–1-infected infants, children, and adolescents. Subjects were stratified by age, enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). All subjects received a weight-based dose of dolutegravir.

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 log10 copies per mL, median CD4+ cell count was 639 cells per mm^3 (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of

subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm^3 in Cohort 1. For Cohort 2A, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm^3.

The safety, virologic, and immunologic responses in subjects who received dolutegravir were evaluated in 46 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 (see section 5.2). Frequency, type, and severity of adverse reactions among the 46 paediatric subjects were comparable to those observed in adults (see section 4.8). In 17 subjects weighing at least 30 kg, pharmacokinetic parameters of dolutegravir were comparable to adults receiving 50 mg once daily (see section 5.2).

Safety and efficacy of dolutegravir have not been established in paediatric patients weighing less than 30 kg or in any paediatric patients who are INSTI-experienced.

Lamivudine

Clinical endpoint trial

ACTG300 was a multicenter, randomized, double-blind trial that provided for comparison of lamivudine plus RETROVIR (zidovudine) with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (less than or equal to 56 days of antiretroviral therapy) paediatric subjects were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-white. The mean baseline CD4+ cell count was 868 cells per mm^3 (mean: 1,060 cells per mm^3 and range: 0 to 4,650 cells per mm^3 for subjects aged less than or equal to 5 years; mean: 419 cells per mm3 and range: 0 to 1,555 cells per mm^3 for subjects aged over 5 years) and the mean baseline plasma HIV-1 RNA was 5.0 log10 copies per mL. The median duration on trial was 10.1 months for the subjects receiving lamivudine plus RETROVIR and 9.2 months for subjects receiving didanosine monotherapy. Results are summarized in Table 27.

Table 27. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus RETROVIR (n = 236)	Didanosine (n = 235)

HIV-1 disease progression or death (total) Physical growth failure Central nervous system deterioration CDC Clinical Category C Death	15 (6.4%) 7 (3.0%) 4 (1.7%) 2 (0.8%) 2 (0.8%)	37 (15.7%) 6 (2.6%) 12 (5.1%) 8 (3.4%) 11 (4.7%)

The safety and effectiveness of lamivudine in combination with other antiretroviral medicinal products have been established in paediatric patients aged 3 months and older. Lamivudine scored tablet is the preferred formulation for HIV-1-infected paediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate because paediatric subjects who received Lamivudine oral solution had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving lamivudine in the ARROW trial (see section 5.2).

Tenofovir disoproxil fumarate

Paediatric Patients 2 Years of Age and Older with HIV-1 infection

The safety of tenofovir disoproxil fumarate in paediatric patients aged 2 to less than 18 years is supported by data from two randomized trials in which tenofovir disoproxil fumarate was administered to HIV-1 infected treatment-experienced subjects. In addition, the pharmacokinetic profile of tenofovir in patients 2 to less than 18 years of age at the recommended doses was similar to that found to be safe and effective in adult clinical trials (see section 5.2).

In Study 352, 92 treatment-experienced subjects 2 to less than 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimen were randomized to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (N=44) or continue their original regimen (N=48) for 48 weeks. Five additional subjects over the age of 12 were enrolled and randomized (tenofovir disoproxil fumarate N=4, original regimen N=1) but are not included in the efficacy analysis. After 48 weeks, all eligible subjects were allowed to continue in the study receiving open-label tenofovir disoproxil fumarate. At Week 48, 89% of subjects in the tenofovir disoproxil fumarate treatment group and 90% of subjects in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations less than 400 copies/mL. During the 48 week randomized phase of the study, 1 subject in the tenofovir disoproxil fumarate group discontinued the study prematurely because of virologic failure/lack of efficacy and 3 subjects (2 subjects in the tenofovir disoproxil fumarate group and 1 subject in the stavudine or zidovudine group) discontinued for other reasons.

In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with tenofovir disoproxil fumarate (N=45) or placebo (N=42) in combination with an optimized

background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm3 and the mean baseline plasma HIV-1 RNA was 4.6 log10 copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir disoproxil fumarate and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir disoproxil fumarate and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir disoproxil fumarate in paediatric patients 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir disoproxil fumarate (see sections 4.4, 4.8, 5.2).

Safety and effectiveness of tenofovir disoproxil fumarate in paediatric patients younger than 2 years of age with HIV-1 infection have not been established.

5.2 Pharmacokinetic properties

Dolutegravir

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 28) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 28. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV–1– Infected Adults

Parameter	50 mg Once Daily Geometric Mean[a] (%CV)	50 mg Twice Daily Geometric Meanb (%CV)
$AUC_{(0\_24)}$ (mcg.h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

a Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

b Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

Lamivudine

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1-infected adult subjects after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg per kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg per kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg per day administered to HBV-infected subjects.

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma AUC24,ss; however, Cmax,ss was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to AUC24,ss and Cmax24,ss; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

The pharmacokinetics of lamivudine was evaluated in 12 adult HIV-1-infected subjects dosed with lamivudine 150 mg twice daily in combination with other antiretroviral medicinal products. The geometric mean (95% CI) for AUC(0-12) was 5.53 (4.58, 6.67) mcg.h per mL and for Cmax was 1.40 (1.17, 1.69) mcg per mL.

Tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir disoproxil fumarate has been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Dolutegravir

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, Cmax, and C24 h ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established.

Lamivudine

the oral powder and tablet formulations.

Effect of food Absolute bioavailability in 12 adult subjects was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 mcg per mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and Cmax increased in proportion to oral dose over the range from 0.25 to 10 mg per kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg per kg twice daily.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted subjects is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. $C_{(MAX)}$ and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not affected by repeated dosing.

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean $C_{(max)\ of}$ tenofovir was 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between

Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets may be taken with or without food.

Distribution

Dolutegravir

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Lamivudine

The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1.3 ± 0.4 L per kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is less than 36%. In vitro studies showed that over the concentration range of 0.1 to 100 mcg per mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Tenofovir disoproxil fumarate

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL. The volume of distribution at steady state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and elimination

Dolutegravir

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

After a single oral dose of [14C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

Lamivudine

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolized by cytochrome P450 enzymes.

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose,

renal clearance was 280.4 ± 75.2 mL per min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life (t½) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg per kg.

Tenofovir disoproxil fumarate

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Specific populations

Paediatric patients

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 17) weighing at least 30 kg were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 29) (see section 5.1).

Table 29. Dolutegravir Steady-State Pharmacokinetic Parameters in Paediatric Subject.

		Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
Weight (n)	Dose of Dolutegravir	C_{Max} (mcg/mL)	$AUC_{(0-24)}$ (mcg.h/mL)	C_{24} (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)

Lamivudine: The pharmacokinetics of lamivudine have been studied after either single or repeat doses of lamivudine in 210 paediatric subjects. Paediatric subjects receiving lamivudine oral solution (dosed at approximately 8 mg per kg per day) achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1-infected adults. Paediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. The absolute bioavailability of both lamivudine tablets and oral solution are lower in children than adults. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in paediatric subjects despite no difference in adults. Lower lamivudine exposures in paediatric patients receiving lamivudine oral solution is likely due to the interaction between lamivudine and concomitant solutions containing sorbitol (such as ZIAGEN). Modeling of pharmacokinetic data suggests increasing the dosage of lamivudine oral solution to 5 mg per kg taken orally twice daily or 10 mg per kg taken orally once daily (up to a maximum of 300 mg daily) is needed to achieve sufficient concentrations of lamivudine. There are no clinical data in HIV-1 infected paediatric patients coadministered with sorbitol-containing medicines at this dose.

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected paediatric subjects aged 2 -12 years was evaluated in 2 trials (PENTA 13 [n = 19], and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice-versus once-daily dosing of abacavir and lamivudine. These 2 trials demonstrated that once-daily dosing provides similar AUC0-24 to twice-daily dosing of lamivudine at the same total daily dose when comparing the dosing regimens within the same formulation (i.e., either the oral solution or the tablet formulation). The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table 30. Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in 2 Paediatric Trials

	Trial (Number of Subjects)			
	ARROW PK (n = 35)		PENTA-13 (n = 19)	
Age Range	3-12 years		2-12 years	
Formulation	Tablet		Solution[a] and Tablet[b]	
Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily
C_{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)
$AUC_{(0-24)}$ (mcg•h/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)

a Solution was dosed at 8 mg per kg per day.

b Five subjects in PENTA-13 received lamivudine tablets.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 paediatric subjects after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg per kg per day, CSF lamivudine concentrations in 8 subjects ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg per mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to paediatric subjects (aged over 3 months) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges over 3 months old.

Tenofovir disoproxil fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 31 HIV-1 infected paediatric subjects 2 to less than 18 years (Table 31). Tenofovir exposure achieved in these paediatric subjects receiving oral once daily doses of tenofovir disoproxil fumarate 300 mg (tablet) was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

Table 31. Mean (± SD) Tenofovir Pharmacokinetic Parameters by Age Groups for HIV-1-infected Paediatric Patients

Dose and Formulation	300 mg Tablet
	12 to <18 Years (N=8)
C_{max} (µg/mL)	0.38 ± 0.13
AUC_{tau} (µg•hr/mL)	3.39 ± 1.22

Tenofovir exposures in 52 HBV-infected paediatric subjects (12 to less than 18 years of age) receiving oral once-daily doses of tenofovir disoproxil fumarate 300 mg tablet were comparable to exposures achieved in HIV-1-infected adults and adolescents receiving once-daily doses of 300 mg.

Elderly

Dolutegravir: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Lamivudine and tenofovir disoproxil fumarate: The pharmacokinetics of lamivudine after administration of lamivudine to subjects over 65 years have not been studied.

Clinical trials of dolutegravir, lamivudine or tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate tablets in elderly patients

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with hepatic impairment has not yet been established.

Dolutegravir: In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Renal impairment

The safety and efficacy of dolutegravir, lamivudine and tenofovir disoproxil fumarate in patients with renal impairment has not yet been established.

Dolutegravir: In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, Cmax, and C24 of dolutegravir were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. The cause of this decrease is unknown. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir has not been studied in patients requiring dialysis.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 33).

Table 33. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion

	(Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC (mcg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment.

Based on a trial in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL per min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

The effects of renal impairment on lamivudine pharmacokinetics in paediatric patients are not known.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir are altered in subjects with renal impairment (see section 4.4). In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{MAX}, and AUC_{0-00} of tenofovir were increased (Table 34). It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.

Table 34. Pharmacokinetic Parameters (Mean ± SD) of Tenofovira in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50–80 (N=10)	30–49 (N=8)	12–29 (N=11)
C_{max} (µg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC0_{0-00}$ (µg·hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

a. 300 mg, single dose of tenofovir disoproxil fumarate

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

HBV or HCV co-infected patients

Dolutegravir: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender

There are no significant or clinically relevant gender differences in dolutegravir, lamivudine or tenofovir disoproxil fumarate pharmacokinetics.

Race

There are no significant or clinically relevant racial differences in dolutegravir or lamivudine pharmacokinetics.

Tenofovir disoproxil fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Pregnancy

Lamivudine: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Drug interaction studies

Dolutegravir

Drug interaction trials were performed with dolutegravir and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of

dolutegravir on the exposure of coadministered drugs are summarized in Table 35 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 36.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 1 (see sections 4.2 and 4.5).

Table 35. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

			Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	-
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	-
Methadone 16 to 150 mg	50 mg twice daily	15[a]	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	-	0.95 (0.79 to 1.15)	-
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)

Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

a The number of subjects represents the maximum number of subjects that were evaluated.

Table 36. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	$C\tau$ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)

Fosamprenavir/ritonavir 700 mg /100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)

Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20	1.17 (1.06 to 1.28)
Rifampina 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

a Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

b Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

c The number of subjects represents the maximum number of subjects that were evaluated.

Lamivudine

Effect of lamivudine on the pharmacokinetics of other agents: Based on in vitro study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of other agents on the pharmacokinetics of lamivudine: Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interferon alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects (see section 4.4).

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18),

stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects (see section 4.4).

Trimethoprim/sulfamethoxazole: Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Tenofovir disoproxil fumarate

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP-mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 37 and 38 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions (Table 38). The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin or sofosbuvir.

Table 37. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovira in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters† (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Ledipasvir/ Sofosbuvir[ef]	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[eg]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[h]	90/400 once daily × 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to↑197)
Ledipasvir/ Sofosbuvir[i]	90/400 once daily × 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir[j]	90/400 once daily × 10 days	29	↑ 61 (↑ 51 to ↑ 72)	↑ 65 (↑ 59 to ↑ 71)	↑ 115 (↑ 105 to ↑ 126)
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir[k]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir[l]	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir[m]	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)

Sofosbuvir/ Velpatasvir[n]	400/100 once daily	15	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)
Sofosbuvir/ Velpatasvir[o]	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir[p]	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[q]	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavirr	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

a. Subjects received tenofovir disoproxil fumarate 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ⇔

c. Reyataz Prescribing Information.

d. Prezista Prescribing Information.

e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.

f. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

g. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) coadministered with HARVONI.

i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) coadministered with HARVONI.

j. Study conducted with TRUVADA (emtricitabine/tenofovir disoproxil fumarate) + dolutegravir coadministered with HARVONI.

k. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).

l. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

m. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate.

n. Study conducted with ATRIPLA coadministered with EPCLUSA (sofosbuvir/velpatasvir).

o. Study conducted with STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) coadministered with EPCLUSA.

p. Study conducted with COMPLERA coadministered with EPCLUSA.

q. Administered as raltegravir + emtricitabine/tenofovir disoproxil fumarate.

r. Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with tenofovir disoproxil fumarate: abacavir, didanosine (buffered tablets), emtricitabine, entecavir, and lamivudine

Table 38. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir disoproxil fumarate

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parametersa (90% CI		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with tenofovir disoproxil	33	↓ 20[g] (↓ 32 to ↓ 7)	⇔[g]	NA

	fumarate and a light meal[f]				
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29h (↑ 12 to ↑ 48) ⇔	↑ 47h (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔
Tipranavir[l]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

d. Prezista Prescribing Information.

e Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.

f. 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

h. Increases in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are coadministered.

i Aptivus Prescribing Information.

5.3 Preclinical safety data

Carcinogenesis

Dolutegravir

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

Tenofovir disoproxil fumarate

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis

Dolutegravir

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Lamivudine

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a

microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

Impairment of Fertility

Dolutegravir

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

Lamivudine

In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir disoproxil fumarate

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

Animal Toxicology and/or Pharmacology

Tenofovir disoproxil fumarate

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Pregnancy and breast-feeding

Dolutegravir

Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on gestation day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the maximum recommended human dose (MRHD) and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

When administered to lactating rats, dolutegravir was present in milk. Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours post-dose.

Lamivudine

Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Tenofovir disoproxil fumarate

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium,

Hydroxy propyl methyl cellulose,

Magnesium stearate,

Mannitol,

Microcrystalline cellulose,

Povidone,Sodium starch glycolate.

Tablet coating

Glycerol esters of fatty acids

FD&C blue #1 (E133),

FD&C blue #2 (E132),

Polyvinyl alcohol-part hydrolysed (E1203),

Sodium lauryl sulfate,

Talc (E553b),

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

For 90's container: Discard 90 days after opening.

6.5 Nature and contents of container

30's container: 85cc white HDPE bottle with 38 mm HDPE Non-CRC cap containing 30 tablets and two 2 gm Silica gel bags.

90’s container: 200cc white HDPE bottle with 45 mm HDPE Non-CRC cap containing 90 tablets and two 2 gm Silica gel bags.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.