Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

ENVUTEG

2. Qualitative and quantitative composition

Each film coated tablet contains:
Dolutegravir sodium equivalent to Dolutegravir 50 mg
Lamivudine USP 300 mg
Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg

Excipient(s) with known effect: Each film coated tablet contains 60.0 mg of Lactose monohydrate.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-Coated Tablet.

A white to off-white, film-coated, capsule shaped, biconvex, beveled edge tablet debossed with **M** on one side of the tablet and **LD** on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age weighing at least 40 kg (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and adolescents aged 12 years and older, weighing at least 40 kg
The recommended dose of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets in adults and adolescents is one tablet once daily.

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should not be administered to adults or

adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of dolutegravir, Tenofovir Alafenamide or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

Missed doses
If the patient misses a dose of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets, the patient should take Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Pregnancy Testing before Initiation of Dolutegravir
Perform pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential.

Elderly
There are limited data available on the use of dolutegravir in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2). Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment
The recommended dose of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min (see section 5.2).

Hepatic impairment
No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available in patients with severe hepatic impairment (Child-Pugh grade C); therefore dolutegravir should be used with caution in these patients (see section 5.2).

Paediatric population
The safety and efficacy of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets in children younger than 12 years of age, or weighing < 40 kg, have not yet been established. No data are available.

Method of administration

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should be taken orally, once daily with or without food (see section 5.2). The film-coated
tablet should not be chewed, crushed, or split.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Co-administration with dofetilide (see section 4.5).

4.4 Special warnings and precautions for use

Embryo-Fetal Toxicity

Preliminary data from an observational study showed that dolutegravir was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of dolutegravir at the time of conception through the first trimester of pregnancy.
If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on dolutegravir, if possible, switch to an alternative regimen.
Perform pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential to exclude use of dolutegravir during the first trimester of pregnancy.
Advise adolescents and adults of childbearing potential to consistently use effective contraception.

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with

dolutegravir or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Patients co-infected with HIV and hepatitis B or C virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established.

Tenofovir alafenamide and lamivudine are active against hepatitis B virus (HBV). Discontinuation of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Liver disease

The safety and efficacy of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets in patients with significant underlying liver disorders have not been established (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and

cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. (See 'Patients with chronic hepatitis B or C' earlier in this section and also see section 4.8).

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Some late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behavior). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Patients with HIV-1 harbouring mutations

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Since the recommended dose of dolutegravir is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is not recommended for patients with integrase inhibitor resistance.

Opportunistic infections

Patients receiving Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and, therefore, should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Co-administration of other medicinal products
Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbital and St. John's wort, the use of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is not recommended for patients taking these medicines (see section 4.5).

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should not be co-administered with polyvalent cation-containing antacids. Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is recommended to be administered 2 hours before or 6 hours after these agents (see section 4.5).

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements (see section 4.5).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control (see section 4.5). Metformin is eliminated renally and therefore it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59

mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

The co-administration of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), boceprevir, St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir (see section 4.5).

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets should not be administered concomitantly with medicinal products containing tenofovir
alafenamide, tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil.

Excipients

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets contains 60.00 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets contains dolutegravir, tenofovir alafenamide and lamivudine, therefore any interactions identified for these individually are relevant to Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300mg/25 mg/50 mg film-coated Tablets. No clinically significant drug interactions are expected between dolutegravir, tenofovir alafenamide and lamivudine.

Lamivudine

Interaction studies have only been performed in adults.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However,

unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section 5.2).

Due to similarities, Lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Lamivudine should not be taken with any other medicinal products containing lamivudine (see section 4.4).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely.

Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC $_{\infty}$) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid chronic co-administration of Lamivudine with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Tenofovir alafenamide

Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide

absorption. Medicinal products that induce P-gp activity (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets and development of resistance. Co-administration of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets with other medicinal products that inhibit P-gp and BCRP activity (e.g., cobicistat, ritonavir, ciclosporin) is expected to increase the absorption and plasma concentration of tenofovir alafenamide.
Based on data from an *in vitro* study, co-administration of tenofovir alafenamide and xanthine oxidase inhibitors (e.g., febuxostat) is not expected to increase systemic exposure to tenofovir *in vivo*.
Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3.

Drug interaction information for Tenofovir alafenamide with potential concomitant medicinal products is summarised in Table below (increase is indicated as "↑", decrease as "↓", no change as "↔"; twice daily as "b.i.d.", single dose as "s.d.", once daily as "q.d."; and intravenously as "IV"). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Tenofovir alafenamide.

Interactions between Tenofovir alafenamide and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}**	**Recommendation concerning co-administration with Tenofovir alafenamide**
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) *Tenofovir* ↓ C_{max} 0.70 (0.65, 0.74) ↔ AUC 0.77 (0.74, 0.81)	Co-administration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.

Midazolam[d] (2.5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.
Midazolamd (1 mg IV, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 0.99 (0.89, 1.11) ↔ AUC 1.08 (1.04, 1.14)	
ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) *Tenofovir* ↔ C_{max} 1.10 (1.00, 1.21) ↔ AUC 1.02 (1.00, 1.04) ↔ C_{min} 1.01 (0.99, 1.03)	No dose adjustment of Tenofovir alafenamide or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (10 mg orally, q.d.)	*Sertraline* ↔ C_{max} 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. *Expected:* ↑ Tenofovir alafenamide	Co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Tenofovir alafenamide or sofosbuvir is required.

Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Ledipasvir* ↔ C_{max} 1.01 (0.97, 1.05) ↔ AUC 1.02 (0.97, 1.06) ↔ C_{min} 1.02 (0.98, 1.07) *Sofosbuvir* ↔ C_{max} 0.96 (0.89, 1.04) ↔ AUC 1.05 (1.01, 1.09) *GS-331007g* ↔ C_{max} 1.08 (1.05, 1.11) ↔ AUC 1.08 (1.06, 1.10) ↔ C_{min} 1.10 (1.07, 1.12) *Tenofovir alafenamide* ↔ C_{max} 1.03 (0.94, 1.14) ↔ AUC 1.32 (1.25, 1.40) *Tenofovir* ↑ C_{max} 1.62 (1.56, 1.68) ↑ AUC 1.75 (1.69, 1.81) ↑ C_{min} 1.85 (1.78, 1.92)	No dose adjustment of Tenofovir alafenamide or ledipasvir/sofosbuvir is required.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Tenofovir alafenamide or sofosbuvir/velpatasvir is required.
Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg[i] orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Sofosbuvir* ↔ C_{max} 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06) *GS-331007g* ↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.04 (1.01, 1.06) *Velpatasvir* ↔ C_{max} 1.05 (0.96, 1.16) ↔ AUC 1.01 (0.94, 1.07) ↔ C_{min} 1.01 (0.95, 1.09) *Voxilaprevir* ↔ C_{max} 0.96 (0.84, 1.11) ↔ AUC 0.94 (0.84, 1.05) ↔ C_{min} 1.02 (0.92, 1.12)	No dose adjustment of Tenofovir alafenamide or sofosbuvir/velpatasvir/voxilapr e vir is required.

	Tenofovir alafenamide ↑ C_{max} 1.32 (1.17, 1.48) ↑ AUC 1.52 (1.43, 1.61)	
HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS		
Atazanavir/cobicistat (300 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.80 (1.48, 2.18) ↑ AUC 1.75 (1.55, 1.98) *Tenofovir* ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.47 (3.29, 3.67) ↑ C_{min} 3.73 (3.54, 3.93) *Atazanavir* ↔ C_{max} 0.98 (0.94, 1.02) ↔ AUC 1.06 (1.01, 1.11) ↔ C_{min} 1.18 (1.06, 1.31) *Cobicistat* ↔ C_{max} 0.96 (0.92, 1.00) ↔ AUC 1.05 (1.00, 1.09) ↑ C_{min} 1.35 (1.21, 1.51)	Co-administration is not recommended.
Atazanavir/ritonavir (300 mg/100 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.77 (1.28, 2.44) ↑ AUC 1.91 (1.55, 2.35) *Tenofovir* ↑ C_{max} 2.12 (1.86, 2.43) ↑ AUC 2.62 (2.14, 3.20) *Atazanavir* ↔ C_{max} 0.98 (0.89, 1.07) ↔ AUC 0.99 (0.96, 1.01) ↔ C_{min} 1.00 (0.96, 1.04)	Co-administration is not recommended.
Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19) *Tenofovir* ↑ C_{max} 3.16 (3.00, 3.33) ↑ AUC 3.24 (3.02, 3.47) ↑ C_{min} 3.21 (2.90, 3.54) *Darunavir* ↔ C_{max} 1.02 (0.96, 1.09) ↔ AUC 0.99 (0.92, 1.07)	Co-administration is not recommended.

	↔ C_{min} 0.97 (0.82, 1.15) *Cobicistat* ↔ C_{max} 1.06 (1.00, 1.12) ↔ AUC 1.09 (1.03, 1.15) ↔ C_{min} 1.11 (0.98, 1.25)	
Darunavir/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.42 (0.96, 2.09) ↔ AUC 1.06 (0.84, 1.35) *Tenofovir* ↑ C_{max} 2.42 (1.98, 2.95) ↑ AUC 2.05 (1.54, 2.72) *Darunavir* ↔ C_{max} 0.99 (0.91, 1.08) ↔ AUC 1.01 (0.96, 1.06) ↔ C_{min} 1.13 (0.95, 1.34)	Co-administration is not recommended.
Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 2.19 (1.72, 2.79) ↑ AUC 1.47 (1.17, 1.85) *Tenofovir* ↑ C_{max} 3.75 (3.19, 4.39) ↑ AUC 4.16 (3.50, 4.96) *Lopinavir* ↔ C_{max} 1.00 (0.95, 1.06) ↔ AUC 1.00 (0.92, 1.09) ↔ C_{min} 0.98 (0.85, 1.12)	Co-administration is not recommended.
Tipranavir/ritonavir	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1.24 (0.88, 1.74) ↑ AUC 1.19 (0.96, 1.48) *Tenofovir* ↔ C_{max} 1.10 (0.96, 1.25) ↑ AUC 1.25 (1.06, 1.47) *Dolutegravir* ↔ C_{max} 1.15 (1.04, 1.27) ↔ AUC 1.02 (0.97, 1.08)	No dose adjustment of Tenofovir alafenamide or dolutegravir is required.

	↔ C_{min} 1.05 (0.97, 1.13)	
Raltegravir	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustmentof or Tenofovir alafenamide raltegravir is required.
HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide[h] (40 mg orally, q.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.78 (0.58, 1.05) ↔ AUC 0.86 (0.72, 1.02) *Tenofovir* ↓ C_{max} 0.75 (0.67, 0.86) ↔ AUC 0.80 (0.73, 0.87) ↔ C_{min} 0.82 (0.75, 0.89) *Expected:* ↔ Efavirenz	No dose adjustmentof or Tenofovir alafenamide efavirenz is required.
Nevirapine	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Nevirapine	No dose adjustmentof or Tenofovir alafenamide nevirapine is required.
Rilpivirine (25 mg orally, q.d.) Tenofovir alafenamide (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.01 (0.84, 1.22) ↔ AUC 1.01 (0.94, 1.09) *Tenofovir* ↔ C_{max} 1.13 (1.02, 1.23) ↔ AUC 1.11 (1.07, 1.14) ↔ C_{min} 1.18 (1.13, 1.23) *Rilpivirine* ↔ C_{max} 0.93 (0.87, 0.99) ↔ AUC 1.01 (0.96, 1.06) ↔ C_{min} 1.13 (1.04, 1.23)	No dose adjustmentof or Tenofovir alafenamide rilpivirine is required.
HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST		
Maraviroc	Interaction not studied. *Expected:* ↔ Tenofovir alafenamide	No dose adjustmentof or Tenofovir alafenamide maraviroc is required.

	↔ Maraviroc	
HERBAL SUPPLEMENTS		
St. John's wort *(hypericum perforatum)*	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
ORAL CONTRACEPTIVES		
Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.) Ethinyl estradiol (0.025 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Norelgestromin* ↔ C_{max} 1.17 (1.07, 1.26) ↔ AUC 1.12 (1.07, 1.17) ↔ C_{min} 1.16 (1.08, 1.24) *Norgestrel* ↔ C_{max} 1.10 (1.02, 1.18) ↔ AUC 1.09 (1.01, 1.18) ↔ C_{min} 1.11 (1.03, 1.20) *Ethinyl estradiol* ↔ C_{max} 1.22 (1.15, 1.29) ↔ AUC 1.11 (1.07, 1.16) ↔ C_{min} 1.02 (0.93, 1.12)	No dose adjustment of Tenofovir alafenamide or norgestimate/ethinyl estradiol is required.

All interaction studies are conducted in healthy volunteers

a. All No Effect Boundaries are 70% - 143%
b. Study conducted with emtricitabine/tenofovir alafenamide fixed-dose combination tablet
c. A sensitive CYP3A4 substrate
d. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet
e. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet
f. The predominant circulating nucleoside metabolite of sofosbuvir
g. Study conducted with tenofovir alafenamide 40 mg and emtricitabine 200 mg
h. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Dolutegravir

Effect of other agents on the pharmacokinetics of dolutegravir

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance.

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of

dolutegravir. Co- administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration.
The absorption of dolutegravir is reduced by certain anti-acid agents (see Table).

Effect of dolutegravir on the pharmacokinetics of other agents
In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).
In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 or MATE-1 (e.g. dofetilide, metformin) (see Table and section 4.3).

In vitro, dolutegravir inhibited the renal uptake transporters, organic anion transporters (OAT1) and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medical products in which excretion is dependent upon OAT3.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table.

Interaction table
Interactions between dolutegravir and co-administered medicinal products are listed in Table (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "$C\tau$").

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors		

Etravirine without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with etravirine without boosted protease inhibitors. In paediatric patients the weight-based once daily dose should be administered twice daily. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients (see further below in table).

Lopinavir/ritonavir + etravirine	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	No dose adjustment is necessary.
Darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	No dose adjustment is necessary.
Efavirenz	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include efavirenz should be considered (see section 4.4).
Nevirapine	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance alternative combinations that do not include nevirapine should be considered (see section 4.4).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitors		

	C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	
Protease Inhibitors		
Atazanavir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Atazanavir/ritonavir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔ (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary. dolutegravir should not be dosed higher than 50 mg twice daily in combination with atazanavir (see section 5.2) due to lack of data.
Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).
Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary in the absence of integrase class resistance. In the presence of integrase class resistance alternative combinations that do not include fosamprenavir/ritonavir should be considered.
Nelfinavir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Tenofovir	Dolutegravir ↔ AUC ↑ 1%	No dose adjustment is necessary.

Darunavir/ritonavir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% C24 ↓ 38% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Lopinavir/ritonavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C24 ↓ 6%	No dose adjustment is necessary.
Other Antiviral agents		
Telaprevir	Dolutegravir ↑ AUC ↑ 25% C_{max} ↑ 19% Cτ ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.
Other agents		
Antiarrhythmics		
Dofetilide	Dofetilide ↑ (Not studied, potential increase via inhibition of OCT2 transporter)	Dolutegravir and dofetilide co-administration is contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration (see section 4.3).
Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.

Azole anti-fungal agents		
Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.
Herbal products		
St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.
Antacids and supplements		
Magnesium/ aluminium-containing antacid	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacid should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C24 ↓ 39% (Complex binding to polyvalent ions)	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of dolutegravir (minimum 2 hours after or 6 hours before).
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C24 ↓ 56% (Complex binding to polyvalent ions)	
Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C24 ↓ 32% (Complex binding to polyvalent ions)	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% C_{τ} ↑ 17%	No dose adjustment is necessary.
Antidiabetics		

Metformin	Metformin ↑ When co-administered with dolutegravir 50mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when co-administered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% C_{τ} ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).

Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% C_{τ} ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Oral contraceptives		
Ethinylestradiol (EE) and Norelgestromin (NGMN)	Dolutegravir ↔ EE ↔ AUC ↑ 3% C_{max} ↓ 1% NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Analgesics		
Methadone	Dolutegravir ↔ Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% C_{τ} ↓ 1%	No dose adjustment is necessary of either agent.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

There are no data on the use of Lamivudine/Tenofovir Alafenamide/Dolutegravir (as sodium) 300 mg/25 mg/50 mg film-coated Tablets in pregnancy.

Lamivudine
Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). Placental transfer of lamivudine has been shown to occur in humans.

More than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Lamivudine can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

Tenofovir Alafenamide
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil fumarate.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

The use of Tenofovir Alafenamide may be considered during pregnancy, if necessary.

Dolutegravir
Risk Summary

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when Dolutegravir is administered at the time of conception compared with non- dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of Dolutegravir at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started Dolutegravir after the first trimester of pregnancy *(see Data)*.
If there are plans to become pregnant or if pregnancy is confirmed while on Dolutegravir during the first trimester, if possible, switch to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to Dolutegravir from the time of conception through the first trimester of pregnancy.
There are insufficient human data on the use of Dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of Dolutegravir *(see Data)*.
Human Data: As of May 2018, in an ongoing birth outcome surveillance study in Botswana, there have been 4 cases of neural tube defects reported out of 426 births (0.94%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.12% (14/11,300) in the non-dolutegravir arm and 0.09% (61/66,057) in the HIV-uninfected arm. Four cases reported with dolutegravir included one case each of encephalocele, anencephaly, myelomeningocele, and iniencephaly. No infant born to a woman who started dolutegravir during pregnancy had a neural tube defect (n = 2,812).
Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.
Animal Data: 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 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 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).

Breast-feeding
It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Lamivudine
Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old.

Tenofovir Alafenamide
It is not known whether tenofovir alafenamide is secreted in human milk. However, in animal studies it has been shown that tenofovir is secreted into milk. There is insufficient information on the effects of tenofovir in newborns/infants.

A risk to the breastfed child cannot be excluded; therefore, Tenofovir Alafenamide should not be used during breast-feeding.

Dolutegravir

Risk Summary

It is not known whether Dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk *(see Data)*.
Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving Dolutegravir.
Data
Animal Data: 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.

Fertility

Lamivudine
Studies in animals showed that lamivudine had no effect on fertility (see section 5.3).

Tenofovir Alafenamide
No human data on the effect of Tenofovir Alafenamide on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

Dolutegravir
Females and Males of Reproductive Potential
Pregnancy Testing
Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of
Dolutegravir. Contraception
Adolescents and adults of childbearing potential should avoid use of Dolutegravir at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects.
Advise adolescents and adults of childbearing potential who are taking Dolutegravir to consistently use effective contraception.

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of dolutegravir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Tenofovir Alafenamide
Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 3,112 HIV-1 infected patients received medicinal products containing emtricitabine and tenofovir alafenamide. In clinical studies of 866 treatment-naïve adult patients receiving emtricitabine and tenofovir alafenamide with elvitegravir and cobicistat as the fixed-dose combination tablet elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (as fumarate) 10 mg (E/C/F/TAF) through 144 weeks, the most frequently reported adverse reactions were diarrhoea (7%), nausea (11%), and headache (6%).

Dolutegravir
The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 1222 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 264 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4). The most commonly seen treatment emergent adverse reactions were nausea (13%), diarrhoea (18%) and headache (13%).

The safety profile was similar across the different treatment populations mentioned above.

Tabulated list of adverse reactions
The adverse reactions considered at least possibly related to Lamivudine, Tenofovir Alafenamide, Dolutegravir are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to
<1/1,000), very rare (<1/10,000).

Adverse reaction

	Frequency	*Lamivudine*	*Tenofovir Alafenamide*	*Dolutegravir*
Blood and lymphatic systems disorders	*Uncommon* *Very rare:*	Neutropenia and Anaemia both occasionally severe), thrombocytopenia Pure red cell aplasia	anaemia[2]	
Immune system disorders	*Uncommon*			Hypersensitivity (see section 4.4), Immune Reconstitution Syndrome (see section 4.4)**
Metabolism and nutrition disorders	*Very rare*	Lactic acidosis		
Nervous system disorders	*Very common*			Headache
	Common	Headache, insomnia	headache, dizziness	Dizziness
	Very rare	Peripheral neuropathy (or paraesthesia)		
Respiratory, Thoracic and mediastinal disorders	*Common*	Cough, nasal symptoms		
Gastrointestinal disorders	*Very common*		nausea	Nausea ,Diarrhoea ,
	Common	Nausea, vomiting, abdominal pain or cramps, diarrhoea	diarrhoea, vomiting, abdominal pain, flatulence	Vomiting, Flatulence, Upper abdominal pain , Abdominal pain ,Abdominal discomfort
	Rare	Pancreatitis, elevations in serum amylase		
	Uncommon		dyspepsia	
Hepatobiliary disorders	*Uncommon*	Transient elevations in liver enzymes (AST, ALT)		Hepatitis
	Rare	Hepatitis		
Skin and subcutaneous tissue disorders	*Common*	Rash, alopecia	rash	Rash ,Pruritus
	Rare	Angioedema		
	Uncommon		angioedema[2,3], pruritus	
Musculoskeletal and connective tissue disorders	*Common*	Arthralgia, muscle disorders		
	Rare	Rhabdomyolysis		
	Uncommon		Arthralgia	Arthralgia ,Myalgia
General disorders and administration site conditions	*Common*	Fatigue, malaise, fever	fatigue	Fatigue

Psychiatric disorders	*Common*		abnormal dreams	Insomnia Abnormal dreams Depression Anxiety
	Uncommon			Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
Investigations	*Common*			Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations . Creatine phosphokinase (CPK) elevations

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency of which is unknown (see section 4.4).

Paediatric population

1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

1. With the exception of angioedema and anaemia (see footnotes 2 and 3), all adverse reactions were identified from clinical studies of F/TAF containing products. The frequencies were derived from Phase 3 E/C/F/TAF clinical studies in 866 treatment-naïve adult patients through 144 weeks of treatment (GS-US-292-0104 and GS-US-292-0111).
2. This adverse reaction was not observed in the clinical studies of F/TAF containing products but identified from clinicalstudies or post-marketing experience for emtricitabine when used with other antiretrovirals.
3. This adverse reaction was identified through post-marketing surveillance for emtricitabine but was not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency

category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n = 1,563).

**see below under Description of selected adverse reactions.

Description of selected adverse reactions

Changes in laboratory biochemistries
Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. A mean change from baseline of 9.96 µmol/L was observed after 48 weeks of treatment. Creatinine increases were comparable by various background regimens. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C
In Phase III studies patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients 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 co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Immune response syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population
Based on limited available data in children and adolescents (6 to less than 18 years of age and weighing at least 15 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

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 national reporting system.

4.9 Overdose

Lamivudine

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Tenofovir Alafenamide

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8).
Treatment of overdose with Tenofovir Alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.
Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

Dolutegravir

There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not assigned, ATC code: Not assigned Namibia Pharmacological Classification: 20.2.8 – Antiviral agents

Lamivudine

Mechanism of action

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'- triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*, it is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects *in vitro* were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Clinical efficacy and safety

In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point

data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors).

Clinical trial evidence from paediatric patients receiving lamivudine with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

Children receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (see the description of the clinical experience in paediatric population (ARROW study) and section 5.2).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretroviral-naive patients as well as in patients presenting with viruses containing the M184V mutations.

The relationship between *in vitro* susceptibility of HIV to lamivudine and clinical response to lamivudine- containing therapy remains under investigation.

Lamivudine at a dose of 100 mg once daily has also been shown to be effective for the treatment of adult patients with chronic HBV infection (for details of clinical studies, see the prescribing information for Zeffix). However, for the treatment of HIV infection only a 300 mg daily dose of lamivudine (in combination with other antiretroviral agents) has been shown to be efficacious.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.

Once daily dosing (300 mg once a day):
A clinical study has demonstrated the non inferiority between Lamivudine once a day and Lamivudine twice a day containing regimens. These results were obtained in an antiretroviral naïve-population, primarily consisting of asymptomatic HIV infected patients (CDC stage A).

Paediatric population:
A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised,

multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/ml	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/ml	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/ml	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of
<80 c/ml at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/ml, <400c/ml, <1000c/ml), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

At the time of randomization to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/ml: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/ml: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughouts	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughouts	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/ml. More cases of resistance were detected among patients who had received lamivudine solution, in combination with other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.

Tenofovir alafenamide

Mechanism of action

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidite prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chaintermination.

Tenofovir has activity against HIV-1, HIV-2, and HBV.

Antiviral activity *in vitro*

The antiviral activity of tenofovir alafenamide against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4+-T lymphocytes. The EC50 values for tenofovir alafenamide were in the range of 2.0 to 14.7 nM. Tenofovir alafenamide displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM).

Resistance

In vitro

HIV-1 isolates with reduced susceptibility to tenofovir alafenamide express a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed.

In treatment-naïve patients

In a pooled analysis of antiretroviral-naïve patients receiving emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet in Phase 3 studies GS- US-292-0104 and GS-US-292-0111, genotyping was performed on plasma HIV-1 isolates from all patients with HIV-1 RNA ≥ 400 copies/mL at confirmed virological failure, at Week 144, or at the time of early study drug discontinuation. Through Week 144, the development of one or more primary emtricitabine, tenofovir alafenamide, or elvitegravir resistance-associated mutations was observed in HIV-1 isolates from 12 of 22 patients with evaluable genotypic data from paired baseline and E/C/F/TAF treatment- failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment-failure isolates from patients with evaluable genotypic data in the E/C/F/TDF group (12 of 867 patients [1.4%]). In the E/C/F/TAF group, the mutations that emerged were M184V/I (n = 11) and K65R/N (n = 2) in RT and T66T/A/I/V (n = 2), E92Q (n = 4), Q148Q/R (n = 1), and N155H (n = 2) in integrase. Of the HIV-1 isolates from 12 patients with resistance development in the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 9), K65R/N (n = 4), and L210W (n = 1) in RT and E92Q/V (n = 4) and Q148R (n = 2), and N155H/S (n=3) in integrase. Most HIV-1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir in integrase also developed resistance mutations to emtricitabine in RT.

In patients co-infected with HIV and HBV

In a clinical study of HIV virologically suppressed patients co-infected with chronic hepatitis B, who received emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF), for 48 weeks (GS-US-292-1249, n = 72), 2 patients qualified for resistance analysis. In these 2 patients, no amino acid substitutions associated with resistance to any of the components of E/C/F/TAF were identified in HIV-1 or HBV.

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients

The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, emtricitabine, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside-resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to tenofovir alafenamide.

Clinical data

There are no efficacy and safety studies conducted in treatment-naïve patients with and tenofovir alafenamide.

Clinical efficacy of and tenofovir alafenamide was established from studies conducted with emtricitabine and tenofovir alafenamide when given with elvitegravir and cobicistat as the fixed-dose combination tablet E/C/F/TAF.

HIV-1 infected, treatment-naïve patients
In studies GS-US-292-0104 and GS-US-292-0111, patients were randomised in a 1:1 ratio to receive either emtricitabine 200 mg and tenofovir alafenamide 10 mg (n = 866) once daily or emtricitabine 200 mg + tenofovir disoproxil (as fumarate) 245 mg (n = 867) once daily, both given with elvitegravir 150 mg + cobicistat 150 mg as a fixed-dose combination tablet. The mean age was 36 years (range: 18-76), 85% were male, 57% were White, 25% were Black, and 10% were Asian. Nineteen percent of patients were identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range: 1.3- 7.0) and 23% had baseline viral loads > 100,000 copies/mL. The mean baseline CD4+ cell count was 427 cells/mm^3 (range: 0-1,360) and 13% had a CD4+ cell count < 200 cells/mm^3.

E/C/F/TAF demonstrated statistical superiority in achieving HIV-1 RNA < 50 copies/mL when compared to E/C/F/TDF at Week 144. The difference in percentage was 4.2% (95% CI: 0.6% to 7.8%). Pooled treatment outcomes at 48 and 144 weeks are shown in Table.

Pooled virological outcomes of Studies GS-US-292-0104 and GS-US-292-0111 at Weeks 48 and 144[a,b]

	Week 48		**Week 144**	
	E/C/F/TAF (n = 866)	**E/C/F/TDF[e] (n = 867)**	**E/C/F/TAF (n = 866)**	**E/C/F/TDF (n = 867)**
HIV-1 RNA < 50 copies/mL	92%	90%	84%	80%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)		4.2% (95% CI: 0.6% to 7.8%)	
HIV-1 RNA ≥ 50 copies/mL[c]	4%	4%	5%	4%
No virologic data at Week 48 or 144 window	4%	6%	11%	16%
Discontinued study drug due to AE or death[d]	1%	2%	1%	3%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	2%	4%	9%	11%
Missing data during window but on study drug	1%	< 1%	1%	1%
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup				
Age < 50 years	716/777 (92%)	680/753 (90%)	647/777 (83%)	602/753 (80%)

≥ 50 years	84/89 (94%)	104/114 (91%)	82/89 (92%)	92/114 (81%)
Sex				
Male	674/733 (92%)	673/740 (91%)	616/733 (84%)	603/740 (81%)
Female	126/133 (95%)	111/127 (87%)	113/133 (85%)	91/127 (72%)
Race				
Black	197/223 (88%)	177/213 (83%)	168/223 (75%)	152/213 (71%)
Non-black	603/643 (94%)	607/654 (93%)	561/643 (87%)	542/654 (83%)
Baseline viral load				
≤ 100,000 copies/mL	629/670 (94%)	610/672 (91%)	567/670 (85%)	537/672 (80%)
> 100,000 copies/mL	171/196 (87%)	174/195 (89%)	162/196 (83%)	157/195 (81%)
Baseline CD4+ cell count				
< 200 cells/mm^3	96/112 (86%)	104/117 (89%)	93/112 (83%)	94/117 (80%)
≥ 200 cells/mm^3	703/753 (93%)	680/750 (91%)	635/753 (84%)	600/750 (80%)
HIV-1 RNA < 20 copies/mL	84.4%	84.0%	81.1%	75.8%
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		5.4% (95% CI: 1.5% to 9.2%)	

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

a. Week 48 window was between Day 294 and 377 (inclusive); Week 144 window was between Day 966 and 1049 (inclusive).
b. In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4+ cell count (< 50 cells/μL, 50-199 cells/μL, or ≥ 200 cells/μL), and by region (US or ex-US).
c. Included patients who had ≥ 50 copies/mL in the Week 48 or 144 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

The mean increase from baseline in CD4+ cell count was 230 cells/mm^3 in patients receiving E/C/F/TAF and 211 cells/mm^3 in patients receiving E/C/F/TDF (p = 0.024) at Week 48, and 326 cells/mm^3 in E/C/F/TAF-treated patients and 305 cells/mm^3 in E/C/F/TDF-treated patients (p = 0.06) at Week 144.

Clinical efficacy of tenofovir alafenamide in treatment-naïve patients was also established from a study conducted with emtricitabine and tenofovir

alafenamide (10 mg) when given with darunavir (800 mg) and cobicistat as a fixed-dose combination tablet (D/C/F/TAF). In Study GS-US-299-0102, patients were randomised in a 2:1 ratio to receive either fixed-dose combination D/C/F/TAF once daily (n = 103) or darunavir and cobicistat and emtricitabine/tenofovir disoproxil fumarate once daily (n = 50). The proportions of patients with plasma HIV-1 RNA < 50 copies/mL and < 20 copies/mL are shown in Table.

Virological outcomes of Study GS-US-299-0102 at Week 24 and 48[a]

	Week 24		**Week 48**	
	D/C/F/TAF (n = 103)	**Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)**	**D/C/F/TAF (n = 103)**	**Darunavir, cobicistat and emtricitabine/tenofovir disoproxil fumarate (n = 50)**
HIV-1 RNA < 50 copies/mL	75%	74%	77%	84%
Treatment difference	3.3% (95% CI: -11.4% to 18.1%)		-6.2% (95% CI: -19.9% to 7.4%)	
HIV-1 RNA ≥ 50 copies/mL[b]	20%	24%	16%	12%
No virologic data at Week 48 window	5%	2%	8%	4%
Discontinued study drug due to AE or death[c]	1%	0	1%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	4%	2%	7%	2%
Missing data during window but on study drug	0	0	0	0
HIV-1 RNA < 20 copies/mL	55%	62%	63%	76%
Treatment difference	-3.5% (95% CI: -19.8% to 12.7%)		-10.7% (95% CI: -26.3% to 4.8%)	

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Included patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
c. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

d. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

HIV-1 infected virologically suppressed patients
In Study GS-US-311-1089, the efficacy and safety of switching from emtricitabine/tenofovir disoproxil fumarate to emtricitabine and tenofovir alafenamide while maintaining the third antiretroviral agent were evaluated in a randomised, double-blind study of virologically suppressed HIV-1 infected adults (n
= 663). Patients must have been stably suppressed (HIV-1 RNA < 50 copies/mL) on their baseline regimen for at least 6 months and had HIV-1 with no resistance mutations to emtricitabine or tenofovir alafenamide prior to study entry. Patients were randomised in a 1:1 ratio to either switch to emtricitabine and tenofovir alafenamide (n = 333), or stay on their baseline emtricitabine/tenofovir disoproxil fumarate containing regimen (n = 330). Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 46% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with a boosted PI and 54% of patients were receiving emtricitabine/tenofovir disoproxil fumarate in combination with an unboosted third agent.

Treatment outcomes of Study GS-US-311-1089 through 48 and 96 weeks are presented in Table.

Virological outcomes of Study GS-US-311-1089 at Weeks 48a and 96[b]

	Week 48		**Week 96**	
	emtricitabine and tenofovir alafenamide containing regimen (n = 333)	**Emtricitabine/ tenofovir disoproxil fumarate containing regimen (n = 330)**	**emtricitabine and tenofovir alafenamide containing regimen (n = 333)**	**Emtricitabine/ tenofovir disoproxil fumarate containing regimen (n = 330)**
HIV-1 RNA < 50 copies/mL	94%	93%	89%	89%
Treatment difference	1.3% (95% CI: -2.5% to 5.1%)		-0.5% (95% CI: -5.3% to 4.4%)	
HIV-1 RNA ≥ 50 copies/mL[c]	< 1%	2%	2%	1%
No virologic data at Week 48 or 96 window	5%	5%	9%	10%
Discontinued study drug due to AE or death[d]	2%	1%	2%	2%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/m L[e]	3%	5%	7%	9%

Missing data during window but on study drug	**< 1%**	**0**	**0**	**<1%**
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen				
Boosted PIs	142/155 (92%)	140/151 (93%)	133/155 (86%)	133/151 (88%)
Other third agents	172/178 (97%)	167/179 (93%)	162/178 (91%)	161/179 (90%)

PI = protease inhibitor

a. Week 48 window was between Day 294 and 377 (inclusive).
b. Week 96 window was between Day 630 and 713 (inclusive).
c. Included patients who had ≥ 50 copies/mL in the Week 48 or Week 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

In Study GS-US-311-1717, patients who were virologically suppressed (HIV-1 RNA <50 copies/mL) on their abacavir/lamivudine containing regimen for at least 6 months were randomised in a 1:1 ratio to either switch to emtricitabine/tenofovir alafenamide (N=280) while maintaining their third agent at baseline or stay on their baseline abacavir/lamivudine -containing regimen (N=276).

Patients were stratified by the class of the third agent in their prior treatment regimen. At baseline, 30% of patients were receiving abacavir/lamivudine in combination with a boosted protease inhibitor and 70% of patients were receiving abacavir/lamivudine in combination with an unboosted third agent. Virologic success rates at Week 48 were: emtricitabine/tenofovir alafenamide Containing Regimen: 89.7% (227 of 253 subjects); Abacavir/lamivudine Containing Regimen: 92.7%% (230 of 248 subjects). At Week 48, switching to a emtricitabine/tenofovir alafenamide -containing regimen was non-inferior to staying on a baseline abacavir/lamivudine-containing regimen in maintaining HIV-1 RNA < 50 copies/mL

HIV-1 infected patients with mild to moderate renal impairment
In Study GS-US-292-0112, the efficacy and safety of emtricitabine and tenofovir alafenamide were evaluated in an open-label clinical study in which 242 HIV-1 infected patients with mild to moderate renal impairment (eGFRCG: 30-69 mL/min) were switched to emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients were

virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months before switching.
The mean age was 58 years (range: 24-82), with 63 patients (26%) who were ≥ 65 years of age. Seventy- nine percent were male, 63% were White, 18% were Black, and 14% were Asian. Thirteen percent of patients were identified as Hispanic/Latino. At baseline, median eGFR was 56 mL/min, and 33% of patients had an eGFR from 30 to 49 mL/min. The mean baseline CD4+ cell count was 664 cells/mm^3 (range: 126-1,813).

At Week 144, 83.1% (197/237 patients) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet.

Patients co-infected with HIV and HBV
In open-label Study GS-US-292-1249, the efficacy and safety of emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet (E/C/F/TAF), were evaluated in adult patients co-infected with HIV-1 and chronic hepatitis B. Sixty-nine of the 72 patients were on prior TDF-containing antiretroviral therapy. At the start of treatment with E/C/F/TAF, the 72 patients had been HIV-suppressed (HIV-1 RNA < 50 copies/mL) for at least 6 months with or without suppression of HBV DNA and had compensated liver function. The mean age was 50 years (range 28-67), 92% of patients were male, 69% were White, 18% were Black, and 10% were Asian. The mean baseline CD4+ cell count was 636 cells/mm^3 (range 263-1498). Eighty-six percent of patients (62/72) were HBV suppressed (HBV DNA < 29 IU/mL) and 42% (30/72) were HBeAg positive at baseline.

Of the patients who were HBeAg positive at baseline, 1/30 (3.3%) achieved seroconversion to anti-HBe at Week 48. Of the patients who were HBsAg positive at baseline, 3/70 (4.3%) achieved seroconversion to anti-HBs Week 48.

At Week 48, 92% of patients (66/72) maintained HIV-1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide, given with elvitegravir and cobicistat as a fixed-dose combination tablet. The mean change from baseline in CD4+ cell count at Week 48 was -2 cells/mm^3. Ninety-two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. Of the 62 patients who were HBV suppressed at baseline, 59 remained suppressed and
3 had missing data. Of the 10 patients who were not HBV suppressed at baseline (HBV DNA ≥ 29 IU/mL), 7 became suppressed, 2 remained detectable, and 1 had missing data.

There are limited clinical data on the use of E/C/F/TAF in HIV/HBV co-infected patients who are treatment-naïve.

Changes in measures of bone mineral density
In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet was associated with smaller reductions in bone mineral density (BMD) compared to

E/C/F/TDF through 144 weeks of treatment as measured by dual energy X ray absorptiometry (DXA) analysis of hip (mean change: −0.8% vs −3.4%, $p < 0.001$) and lumbar spine (mean change: −0.9% vs −3.0%, $p < 0.001$). In a separate study, emtricitabine and tenofovir alafenamide given with darunavir and cobicistat as a fixed-dose combination tablet was also associated with smaller reductions in BMD (as measured by hip and lumbar spine DXA analysis) through 48 weeks of treatment compared to darunavir, cobicistat, emtricitabine and tenofovir disoproxil fumarate.

In a study in virologically suppressed adult patients, improvements in BMD were noted through 96 weeks after switching to emtricitabine/tenofovir alafenamide from a TDF containing regimen compared to minimal changes with maintaining the TDF containing regimen as measured by DXA analysis of hip (mean change from baseline of 1.9% vs -0.3%, $p < 0.001$) and lumbar spine (mean change from baseline of 2.2% vs -0.2%, $p < 0.001$).

In a study in virologically suppressed adult patients, BMD did not change significantly through 48 weeks after switching to emtricitabine/tenofovir alafenamide from an abacavir/lamivudine containing regimen compared to maintaining the abacavir/lamivudine containing regimen as measured by DXA analysis of hip (mean change from baseline of 0.3% vs 0.2%, $p = 0.55$) and lumbar spine (mean change from baseline of
0.1% vs < 0.1%, $p = 0.78$).

Changes in measures of renal function
In studies in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet through 144 weeks was associated with a lower impact on renal safety parameters (as measured after 144 weeks treatment by eGFRCG and urine protein to creatinine ratio and after 96 weeks treatment by urine albumin to creatinine ratio) compared to E/C/F/TDF. Through 144 weeks of treatment, no subject discontinued E/C/F/TAF due to a treatment- emergent renal adverse event compared with 12 subjects who discontinued E/C/F/TDF ($p < 0.001$).

In a separate study in treatment-naïve patients, emtricitabine and tenofovir alafenamide given with darunavir and cobicistat as a fixed-dose combination tablet was associated with a lower impact on renal safety parameters through 48 weeks of treatment compared to darunavir and cobicistat given with emtricitabine/tenofovir disoproxil fumarate (see also section 4.4).

In a study in virologically suppressed adult patients measures of tubular proteinuria were similar in patients switching to a regimen containing emtricitabine/tenofovir alafenamide compared to patients who stayed on an abacavir/lamivudine containing regimen at baseline.

At Week 48, the median percentage change in urine retinol binding protein to creatinine ratio was 4% in the emtricitabine/tenofovir alafenamide group and 16% in those remaining on an abacavir/lamivudine containing regimen; and in urine beta-2 microglobulin to creatinine ratio it was 4% vs. 5%.

Paediatric population
In Study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in an open-label study in which 50 HIV-1 infected, treatment-naïve adolescents received emtricitabine and tenofovir alafenamide (10 mg) given with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a mean age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL, median CD4+ cell count was 456 cells/mm^3 (range: 95-1,110), and median CD4+% was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA > 100,000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA < 50 copies/mL, similar to response rates in studies of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. No emergent resistance to E/C/F/TAF was detected through Week 48.

Dolutegravir

Mechanism of action
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. Pharmacodynamic effects

Antiviral activity in cell culture
The IC50 for dolutegravir in various labstrains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC50s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC50 value was 0.2 nM (range 0.02-2.14). The mean IC50 for 3 HIV-2 isolates was 0.18 nM (range 0.09- 0.61).

Antiviral activity in combination with other antiviral agents
No antagonistic effects *in vitro* were seen with dolutegravir and other antiretrovirals tested: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc and raltegravir. In addition, no antagonistic effects were seen for dolutegravir and adefovir, and ribavirin had no apparent effect on dolutegravir activity.

Effect of human serum
In 100% human serum, the mean protein fold shift was 75 fold, resulting in protein adjusted IC90 of
0.064 ug/mL.

Resistance
Resistance in vitro
Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIV-1 IIIB during passage over 112 days, mutations selected appeared

slowly, with substitutions at positions S153Y and F, resulting in a maximal fold change in susceptibility of 4 (range 2-4). These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432, mutations E92Q (FC 3) and G193E (also FC 3) were selected. The E92Q mutation has been selected in patients with pre-existing raltegravir resistance who were then treated with dolutegravir (listed as a secondary mutation for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two ART experienced, INI naive individual patients with subtypes B and C in the clinical program, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was not detected in patients receiving dolutegravir in the Phase III program.
Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q and T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to these primary mutations in experiments with site directed mutants, dolutegravir susceptibility is still unchanged (FC <2 vs wild type virus), except in the case of Q148-mutations, where a FC of 5-10 or higher is seen with combinations of certain secondary mutations. The effect by the Q148-mutations (H/R/K) was also verified in passage experiments with site directed mutants. In serial passage with strain NL432, starting with site directed mutants harbouring N155H or E92Q, no further selection of resistance was seen (FC unchanged around 1). In contrast, starting with mutants harbouring mutation Q148H (FC 1), a variety of secondary mutations were seen with a consequent increase of FC to values >10.

A clinically relevant phenotypic cut-off value (FC vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a less than or equal to 10 FC against 94% of the 705 clinical isolates.

Resistance in vivo

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48- 96 weeks).

In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum FC of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

In the presence of integrase class-resistance (VIKING-3 study) the following mutations were selected in 32 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimized background agents): L74L/M (n=1), E92Q (n=2), T97A (n=9), E138K/A/T (n=8), G140S (n=2), Y143H (n=1), S147G (n=1), Q148H/K/R (n=4), and N155H (n=1) and E157E/Q (n=1).

Treatment emergent integrase resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic). Five further subjects experienced PDVF between weeks 24 and 48, and 2 of these 5 had treatment emergent mutations. Treatment- emergent mutations or mixtures of mutations observed were L74I (n=1), N155H (n=2).

The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study.

Effects on electrocardiogram
No relevant effects were seen on the QTc interval, with doses exceeding the clinical dose by approximately three fold.

Clinical efficacy and safety

Previously untreated patients
The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and activecontrolled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks.

In SPRING-2, 822 adults were randomized and received at least one dose of either dolutegravir 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 36 years, 14% were female, 15% non-white, 11% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least one dose of either dolutegravir 50 mg once daily with fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% nonwhite, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.
The primary endpoint and other week 48 outcomes (including outcomes by key baseline covariates) for SPRING-2 and SINGLE are shown in Table.

Response in SPRING-2 and SINGLE at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	SPRING-2		**SINGLE**	
	Dolutegravir 50 mg Once Daily + 2 NRTI N=411	**RAL 400 mg Twice Daily + 2 NRTI N=411**	**Dolutegravir 50 mg + ABC/3TC Once Daily N=414**	**EFV/TDF/FTC Once Daily N=419**
HIV-1 RNA <50 copies/mL	88%	85%	88%	81%
Treatment Difference*	2.5% (95% CI: -2.2%, 7.1%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic non-response†	5%	8%	5%	6%
HIV-1 RNA <50 copies/mL by baseline covariates				
Baseline Viral Load (cps/mL)				
≤100,000 >100,000	267 / 297 (90%) 94 / 114 (82%)	264 / 295 (89%) 87 / 116 (75%)	253 / 280 (90%) 111 / 134 (83%)	238 / 288 (83%) 100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)				
<200 200 to <350 ≥350	43 / 55 (78%) 128 / 144 (89%) 190 / 212 (90%)	34 / 50 (68%) 118 / 139 (85%) 199 / 222 (90%)	45 / 57 (79%) 143 / 163 (88%) 176 / 194 (91%)	48 / 62 (77%) 126 / 159 (79%) 164 / 198 (83%)
NRTI backbone				
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	N/A	N/A
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	N/A	N/A
Gender				
Male Female	308 / 348 (89%) 53 / 63 (84%)	305 / 355 (86%) 46 / 56 (82%)	307 / 347 (88%) 57 / 67 (85%)	291 / 356 (82%) 47 / 63 (75%)
Race				
White African-America/African	306 / 346 (88%) 55 / 65 (85%)	301 / 352 (86%) 50 / 59 (85%)	255 / 284 (90%) 109 / 130 (84%)	238 /285 (84%) 99 / 133 (74%)
Heritage/Other				
Age (years)				
<50	324/370 (88%)	312/365 (85%)	319/361 (88%)	302/375 (81%)
≥50	37/41 (90%)	39/46 (85%)	45/53 (85%)	36/44 (82%)
Median CD4 change from baseline	230	230	246‡	187‡

* Adjusted for baseline stratification factors.
† Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Adjusted mean treatment difference was statistically significant (p<0.001)

At week 48, dolutegravir was non-inferior to raltegravir in the SPRING-2 study, and in the SINGLE study dolutegravir + ABC/3TC was superior to efavirenz/TDF/FTC (p=0.003), table above. In SINGLE, the median time to

viral suppression was shorter in the dolutegravir treated patients (28 vs 84 days, ($p<0.0001$, analysis pre-specified and adjusted for multiplicity).

At week 96, results were consistent with those seen at week 48. In SPRING-2, dolutegravir was still noninferior to raltegravir (viral suppression in 81% vs 76% of patients), and with a median change in CD4 count of 276 vs 264 cells/mm^3, respectively. In SINGLE, dolutegravir + ABC/3TC was still superior to EFV/TDF/FTC (viral suppression in 80% vs 72%, treatment difference 8.0% (2.3, 13.8), p=0.006, and with an adjusted mean change in CD4 count of 325 vs 281 cells/ mm^3, respectively. At 144 weeks in the openlabel phase of SINGLE, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).

In FLAMINGO (ING114915), an open-label, randomised and active-controlled study, 484 HIV-1 infected antiretroviral naïve adults received one dose of either dolutegravir 50 mg once daily (n=242) or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily (n=242), both administered with either ABC/3TC or TDF/FTC. At baseline, median patient age was 34 years, 15% were female, 28% non-white, 10% had hepatitis B and/or C co-infection, and 3% were CDC Class C; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir group (90%) was superior to the DRV/r group (83%) at 48 weeks. The adjusted difference in proportion and 95% CI were 7.1% (0.9, 13.2), p=0.025. At 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [DTG-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2].

Treatment emergent resistance in previously untreated patients failing therapy

Through 96 weeks in SPRING-2 and FLAMINGO and 144 weeks in SINGLE, no cases of treatment emergent primary resistance to the integrase- or NRTI-class were seen in the dolutegravir-containing arms. For the comparator arms, the same lack of treatment emergent resistance was also the case for patients treated with darunavir/r in FLAMINGO. In SPRING-2, four patients in the RAL-arm failed with major NRTI mutations and one with raltegravir resistance; in SINGLE, six patients in the EFV/TDF/FTC- arm failed with mutations associated with NNRTI resistance, and one developed a major NRTI mutation.

Patients with prior treatment failure, but not exposed to the integrase class

In the international multicentre, double-blind SAILING study (ING111762), 719 HIV-1 infected, antiretroviral therapy (ART)-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 baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All patients had at least

two class ART resistance, and 49% of subjects had at least 3- class ART resistance at baseline.

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table.

Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Dolutegravir 50 mg Once Daily + BR N=354§	**RAL 400 mg Twice Daily + BR N=361§**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
HIV-1 RNA <50 copies/mL by baseline covariates		
Baseline Viral Load (copies/mL)		
≤50,000 copies/mL >50,000 copies/mL	186 / 249 (75%) 65 / 105 (62%)	180 / 254 (71%) 50 / 107 (47%)
Baseline CD4+ (cells/ mm^3**)**		
<50 50 to <200 200 to <350 ≥350	33 / 62 (53%) 77 / 111 (69%) 64 / 82 (78%) 77 / 99 (78%)	30 / 59 (51%) 76 / 125 (61%) 53 / 79 (67%) 71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2 Genotypic Susceptibility Score* =2 **Use of DRV in background regimen** No DRV use DRV use with primary PI mutations DRV use without primary PI mutations	155 / 216 (72%) 96 / 138 (70%) 143 / 214 (67%) 58 / 68 (85%) 50 / 72 (69%)	129 / 192 (67%) 101 / 169 (60%) 126 / 209 (60%) 50 / 75 (67%) 54 / 77 (70%)
Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
Race		
White	133 / 178 (75%)	125 / 175 (71%)
African-America/African Heritage/Other	118 / 175 (67%)	105 / 185 (57%)
Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm^3)	162	153

‡ Adjusted for baseline stratification factors.
§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site
*The Genotypic Susceptibility Score (GSS) was defined as the total number of ARTs in BR to which a subject's viral isolate showed susceptibility at baseline based upon genotypic resistance tests.
†Other
clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Dolutegravir arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Dolutegravir (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003) (refer to section 'Resistance in vivo' above for details).

Patients with prior treatment failure that included an integrase inhibitor (and integrase class resistance)
In the multicenter, open-label, single arm VIKING-3 study (ING112574), HIV-1 infected, ART-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 but with optimised background ART from Day 8. The study enrolled 183 patients, 133 with INI- resistance at Screening and 50 with only historical evidence of resistance (and not at Screening). Raltegravir/elvitegravir was part of the current failing regimen in 98/183 patients (part of prior failing therapies in the others).

At baseline, median patient age was 48 years, 23% were female, 29% non-white, and 20% had hepatitis B and/or C co-infection. Median baseline CD4+ was 140 cells/mm^3, median duration of prior ART was 14 years, and 56% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major mutations; 62% had non- R5 virus.

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4log_{10} copies/mL (95% CI - 1.3– -1.5log_{10}, p<0.001). Response was associated with baseline INI mutation pathway, as shown in Table.

Virologic response (day 8) after 7 days of functional monotherapy, in patients with RAL/EVG as part of current failing regimen, VIKING 3

Baseline parameters	DTG 50 mg BID N=88*		
	n	Mean (SD) Plasma HIV-1 RNA log_{10} c/mL	Median
Derived IN mutation group at Baseline with ongoing RAL/EVG			
Primary mutation other than Q148H/K/R[a]	48	-1.59 (0.47)	-1.64
Q148+1 secondary mutation[b]	26	-1.14 (0.61)	-1.08
Q148+≥2 secondary mutations[b]	14	-0.75 (0.84)	-0.45

*Of 98 on RAL/EVG as part of current failing regimen, 88 had detectable primary INI mutations at Baseline and a Day 8 Plasma HIV-1 RNA outcome for evaluation

a. Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q
b. Secondary mutations from G140A/C/S, E138A/K/T, L74I.

In patients without a primary mutation detected at baseline (N=60) (i.e. RAL/EVG not part of current failing therapy) there was a 1.63 log_{10} reduction in viral load at day 8.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. The overall response rate through 24 weeks of therapy, 69% (126/183), was generally sustained through 48 weeks with 116/183 (63%) of patients with HIV-1 RNA <50c/mL (ITT-E, Snapshot algorithm). When excluding patients who stopped therapy for non-efficacy reasons, and those with major protocol deviations (incorrect dolutegravir dosing, intake of prohibited co-medication), namely, "the Virological Outcome (VO)-population)", the corresponding response rates were 75% (120/161, week 24) and 69% (111/160, week 48).

The response was lower when the Q148-mutation was present at baseline, and in particular in the presence of ≥2 secondary mutations, below Table. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Response by baseline Resistance, VIKING-3. VO Population (HIV-1 RNA <50 c/mL, Snapshot algorithm)

	Week 24 (N=161)					**Week 48 (N=160)**
Derived IN Mutation						**Total**
Group	**OSS=0**	**OSS=1**	**OSS=2**	**OSS>2**	**Total**	
No primary IN mutation1					45/55	38/55
	2/2 (100%)	15/20 (75%)	19/21 (90%)	9/12 (75%)	(82%)	(69%)
Primary mutation other than Q148H/K/R2	2/2 (100%)	20/20 (100%)	21/27 (78%)	8/10 (80%)	51/59 (86%)	50/58 (86%)
Q148 + 1 secondary mutation3	2/2 (100%)	8/12 (67%)	10/17 (59%)	-	20/31 (65%)	19/31 (61%)
Q148 +≥2 secondary mutations 3	1/2 (50%)	2/11 (18%)	1/3 (33%)	-	4/16 (25%)	4/16 (25%)

1. Historical or phenotypic evidence of INI resistance only. 2. N155H, Y143C/H/R, T66A, E92Q
3. G140A/C/S, E138A/K/T, L74I
OSS: combined genotypic and phenotypic resistance (Monogram Biosciences Net Assessment)

The median change in CD4+ T cell count from baseline for VIKING-3 based on observed data was 61 cells/mm^3 at Week 24 and 110 cells/mm^3 at Week 48.

In the double blind, placebo controlled VIKING-4 study (ING116529), 30 HIV-1 infected, ART-experienced adults with primary genotypic resistance to INIs at Screening, were randomised to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days followed by an open label phase with all subjects receiving dolutegravir. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm^3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at baseline.

The primary endpoint at Day 8 showed that dolutegravir 50 mg twice daily was superior to placebo, with an adjusted mean treatment difference for the change from Baseline in Plasma HIV-1 RNA of -1.2 log_{10} copies/mL (95% CI -1.5 - - 0.8log_{10} copies/mL, p<0.001). The day 8 responses in this placebo controlled study were fully in line with those seen in VIKING-3 (not placebo controlled), including by baseline integrase resistance categories. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm).

In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 126/186 (68%). The proportion of subjects with HIV RNA
<50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+≥2 secondary mutations.

Paediatric population
In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of Dolutegravir has been evaluated in combination regimens in HIV 1 infected, treatment-experienced, INI naive children and adolescents (6 to less than 18 years of age). Subjects were stratified by age, receiving Dolutegravir (70 mg, as 35 mg twice daily, n=1; 50 mg once daily, n=5; 35 mg once daily, n=6; 25 mg once daily, n= 8; and 20 mg once daily, n=3) plus OBR.

Virologic (Snapshot algorithm) and Immunologic Activity of Treatment for Subjects 6 Years and Older in P1093

	Dolutegravir ~1 mg/kg Once Daily + OBR	
	Cohort I (12 to <18 years) (n=23)	Cohort IIA (6 to <12 years) (n=23)
HIV-1 RNA <50 copies/mL at 24 weeks, n (%)	16 (70%)	14 (61%)
HIV-1 RNA <50 copies/mL at 48 weeks, n (%)	14 (61%)	-
HIV-1 RNA <400 copies/mL at 24 weeks, n (%)	19 (83%)	18 (78%)
HIV-1 RNA <400 copies/mL at 48 weeks, n (%)	17 (74%)	-
Virologic non response	6	3
CD4+ Cell Count Median Change from Baseline, cells/mm^3 Median Percent Change from Baseline	84[a] 5%[a]	209[b] 8%[b]

1. 22 subjects contributed Week 48 CD4+ cell count data
2. 21 subjects contributed Week 24 CD4+ cell count data

5.2 Pharmacokinetic properties

Mylan has executed Single-Dose Fasting and Fed Bioequivalence Studies of Lamivudine, Tenofovir Alafenamide and Dolutegravir Tablets (300 mg/25 mg/50 mg; Mylan) versus EPIVIR® Tablets (300 mg; ViiV), VEMLIDY® Tablets (25 mg; Gilead) and TIVICAY® Tablets (50 mg; ViiV) in Healthy Adult Volunteers. These studies demonstrate that Mylan's lamivudine, tenofovir alafenamide and dolutegravir tablets, 300 mg/25 mg/50 mg are bioequivalent under fasting and fed conditions and the summary results are tabulated below:

Dose (1 x 300 mg/25 mg/50 mg)						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Number LTAD-16076), Lamivudine						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	11752	76	12213	76	0.96	92.54% – 100.07%
AUC_{∞} (ng/mL•hr)	12046	76	12509	76	0.96	92.90% – 99.82%
C_{max} (ng/mL)	2411	76	2601	76	0.93	88.37% – 97.21%
Fasting Bioequivalence Study (Study Number LTAD-16076), Tenofovir Alafenamide						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	141.7	76	148.4	76	0.96	89.42% – 101.99%
AUC_{∞} (ng/mL•hr)	144.3	75	150.8	75	0.96	89.55% – 102.23%
C_{max} (ng/mL)	195.5	76	230.6	76	0.85	77.00% – 93.38%
Fasting Bioequivalence Study (Study Number LTAD-16076), Dolutegravir						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	52495	76	50866	76	1.03	98.05% – 108.62%
AUC_{∞} (ng/mL•hr)	54353	76	52588	76	1.03	98.35% – 108.61%
C_{max} (ng/mL)	2776	76	2695	76	1.03	97.77% – 108.55%

*Ratio (A/B) = e [LSMEAN of LNA - LSMEAN of LNB];
**Used Natural Log Transformed Parameter

Dose (1 x 300 mg/25 mg/50 mg)						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study Number LTAD-16077), Lamivudine						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	10821	76	10632	76	1.02	99.26% – 104.34%
AUC_{∞} (ng/mL•hr)	11094	76	10905	76	1.02	99.30% – 104.23%
C_{max} (ng/mL)	1960	76	1883	76	1.04	99.67% – 108.72%
Fed Bioequivalence Study (Study Number LTAD-16077), Tenofovir Alafenamide						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	212.8	76	221.4	76	0.96	87.78% – 105.33%
AUC_{∞} (ng/mL•hr)	240.3	50	235.9	65	1.02	93.60% – 110.80%
C_{max} (ng/mL)	156.8	76	157.7	76	0.99	85.50% – 115.57%
Fed Bioequivalence Study (Study Number LTAD-16077), Dolutegravir						
Parameter	**Test**	**N**	**Reference**	**N**	**Ratio***	**90% C.I.****
AUC_{0-t} (ng/mL•hr)	73262	76	69508	76	1.05	102.19% – 108.71%
AUC_{∞} (ng/mL•hr)	75152	76	71381	76	1.05	102.14% – 108.53%
C_{max} (ng/mL)	3738	76	3436	76	1.09	105.92% – 111.69%

*Ratio (A/B) = e [LSMEAN of LNA - LSMEAN of LNB]
**Used Natural Log Transformed Parameter

Tenofovir Alafenamide (Study Number LTAD-16076)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**S2wr**	**sWR**	**Criteria Bound**	**Method Used**	**Outcome**
$LNAUC_t$	0.96	89.96	101.38	0.0647	0.2543	N/A	ABE	N/A
$LNAUC_i$	0.94	88.9	100.14	0.0655	0.2559	N/A	ABE	N/A
LNC_{max}	0.85	77.88	92.32	0.1416	0.3763	-0.0378	SABE	Pass
Tenofovir Alafenamide (Study Number LTAD-16077)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**S2wr**	**sWR**	**Criteria Bound**	**Method Used**	**Outcome**
$LNAUC_t$	0.96	87.78	105.33	0.0644	0.2538	N/A	ABE	N/A
$LNAUC_i$	0.98	89.72	106.68	0.051	0.2257	N/A	ABE	N/A
LNC_{max}	0.99	85.5	115.57	0.2296	0.4792	-0.128	SABE	Pass

Statistical analyses of these data reveal that the 90% confidence intervals are within the acceptable bioequivalent range of 80.00% and 125.00% for the natural log transformed parameters, $LNAUC_l$, $LNAUC_{inf}$ and LNC_{peak} for lamivudine and dolutegravir and for $LNAUC_l$ and $LNAUC_{inf}$ for tenofovir alafenamide. The intrasubject variability (%ISCV) for the primary pharmacokinetic parameters CPEAK was ≥ 30. Therefore, bioequivalence was assessed using the reference scaled average bioequivalence approach. The 95% upper confidence bound for $((\mu T - \mu R)2/\sigma 2WR)$ is ≤ θ, or equivalently, a 95% upper confidence bound for $(\mu T - \mu R)2 - \theta\ \sigma 2WR$ is ≤ 0 and the point estimate (test/reference geometric mean ratio) falls within 0.80 and 1.25 for LNC_{peak} for tenofovir alafenamide.

Lamivudine

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150 mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 µg/ml (24%) and 0.09 µg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 µg.h/ml (18%). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 µg.h/ml (21%), respectively.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_∞, C_{max}, and t_{max}**.** Administration of Lamivudine tablets is bioequivalent to Lamivudine oral solution with respect to AUC_∞ and C_{max} in adults. Absorption differences have been observed between adult and paediatric populations (see Special populations).

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C max (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Distribution
From intravenous studies, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%) via the organic cationic transport system.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16% - 36% to serum albumin in *in vitro* studies).

Limited data show that lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation
The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, Lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady- state to Lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10%) and low plasma protein binding.

Elimination
Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section (see section 4.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Special populations

Children
The absolute bioavailability of lamivudine (approximately 58-66%) was reduced in paediatric patients below 12 years of age.

In children, administration of tablets given concomitantly with other antiretroviral tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution given concomitantly with other antiretroviral oral solutions. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see section 4.2). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and paediatric exposure, an appropriate dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, an appropriate dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Stead-State Plasma Lamivudine $AUC_{(0-24)}$ (μg.h/ml) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Lamivudine 8mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% CI)

ARROW PK Substudy Part 1	3 to 12 years (N=35)	13.0 (11.4,14.9)	12.0 (10.7, 13.4)	1.09 (0.979, 1.20)
PENTA 13	2 to 12 years (N=19)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	1.12 (1.03, 1.21)
PENTA 15	3 to 36 months (N=17)	8.66 (7.46, 10.1)	9.48 (7.89, 11.40)	0.91 (0.79, 1.06)

In PENTA 15 study, the geometric mean plasma lamivudine $AUC_{(0-24)}$ (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see section 5.1) are 10.31 (6.26, 17.0) µg.h/ml in the once-daily dosing and 9.24 (4.66, 18.3) µg.h/ml in the twice-daily dosing.

Pregnancy
Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non- pregnant women.

Tenofovir alafenamide

Absorption
Following administration of food in healthy subjects, peak plasma concentrations were observed approximately 1 hour post-dose for tenofovir alafenamide administered as F/TAF (25 mg) or E/C/F/TAF (10 mg). The mean C_{max} and AUC_{last}, (mean ± SD) under fed conditions following a single 25 mg dose of tenofovir alafenamide administered in emtricitabine/tenofovir were 0.21 ± 0.13 µg/mL and 0.25 ± 0.11 µg•h/mL, respectively. The mean C_{max} and AUC_{last} following a single 10 mg dose of tenofovir alafenamide administered in E/C/F/TAF were 0.21 ± 0.10 µg/mL and 0.25 ± 0.08 µg•h/mL, respectively.

Relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in tenofovir alafenamide C_{max} (15-37%) and an increase in AUC_{last} (17-77%).

Distribution
In vitro binding of tenofovir to human plasma proteins is < 0.7% and is independent of concentration over the range of 0.01-25 µg/mL. *Ex vivo* binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%.

Biotransformation
Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolised to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of tenofovir alafenamide (given with emtricitabine and elvitegravir and cobicistat) resulted in tenofovir

diphosphate concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of tenofovir in plasma as compared to a 245 mg oral dose of tenofovir disoproxil (as fumarate) (given with emtricitabine and elvitegravir and cobicistat).

In vitro, tenofovir alafenamide is not metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolised by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, tenofovir alafenamide exposure was not significantly affected. Following administration of tenofovir alafenamide, plasma [14C]-radioactivity showed a time-dependent profile with tenofovir alafenamide as the most abundant species in the initial few hours and uric acid in the remaining period.

Elimination
Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion.

Pharmacokinetics in special populations
Age, gender, and ethnicity
No clinically relevant pharmacokinetic differences due to age, gender or ethnicity have been identified for emtricitabine, or tenofovir alafenamide.

Paediatric population
Exposures of emtricitabine and tenofovir alafenamide (given with elvitegravir and cobicistat) achieved in 24 paediatric patients aged 12 to < 18 years who received emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat in Study GS-US-292-0106 were similar to exposures achieved in treatment-naïve adult.

Pharmacokinetics of emtricitabine and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents			**Adults**		
	FTC[a]	TAF[b]	TFV[b]	FTC[a]	TAF[c]	TFV[c]
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
Cmax (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
Ctau (ng/mL)	102.4 (38.9)[b]	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate FTC = emtricitabine; TAF = tenofovir alafenamide fumarate; TFV = tenofovir
N/A = not applicable
Data are presented as mean (%CV).

a. n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)
b. n = 23 adolescents (GS-US-292-0106, population PK analysis)
c. n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Renal impairment
No clinically relevant differences in tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of tenofovir alafenamide. There are no pharmacokinetic data on tenofovir alafenamide in patients with estimated CrCl < 15 mL/min. Mean systemic emtricitabine exposure was higher in patients with severe renal impairment (CrCl < 30 mL/min) (33.7 µg•h/mL) than in subjects with normal renal function (11.8 µg•h/mL).

Hepatic impairment
The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function.

When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

Hepatitis B and/or hepatitis C virus co-infection
The pharmacokinetics of emtricitabine and tenofovir alafenamide have not been fully evaluated in patients co-infected with HBV and/or HCV.

Dolutegravir

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is low to moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC and C_{max} ranged from ~20 to 40% and C_{τ} from 30 to 65% across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw%) is lower than between-subject variability.

Bioequivalence has not been unequivocally shown for 1x50 mg tablet compared to 5x10 mg tablets. Therefore, the 50 mg once daily dose should not be given as five 10 mg tablets.

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation.

Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, Dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance (see section 4.2).

The absolute bioavailability of dolutegravir has not been established.

Distribution
Dolutegravir is highly bound (>99%) to human plasma proteins based on *in vitro* data. The apparent volume of distribution is 17 L to 20 L in HIV-infected patients, based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50).

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation
Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Drug interactions
In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine
diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Elimination
Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

Linearity/non-linearity
The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.
Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

PK/PD modelling using pooled data from clinical studies in integrase resistant patients suggest that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of
dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA <50 c/mL) at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi class resistance. There is no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co- treatment with atazanavir increases the exposure of dolutegravir

markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.

Special patient populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to <18 years of age) showed that Dolutegravir 50 mg once daily oral dosage resulted in dolutegravir exposure comparable to that observed in adults who received Dolutegravir 50 mg orally once daily. The pharmacokinetics was evaluated in 11 children 6 to 12 years of age and showed that 25 mg once daily in patients weighing at least 20 kg and 35 mg once daily in patients weighing at least 30 kg resulted in dolutegravir exposure comparable to adults. In addition, population PK modelling and simulation analyses showed dosing of Dolutegravir tablets on a weight-band basis (20 mg, 25 mg, 35 mg, 50 mg) in children of at least 6 years of age weighing at least 15 kg provides comparable exposure to that observed in adults (50 mg), with the lowest weight band of 15 to <20 kg corresponding to 20 mg daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir in subjects >65 years of age are limited.

Renal impairment

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis.

Hepatic impairment

Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, 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).

Gender
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

Race
Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

Co-infection with Hepatitis B or C
Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited data on subjects with hepatitis B co- infection.

5.3 Preclinical safety data

Lamivudine

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs and showed evidence of more

telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

A fertility study in rats has shown that lamivudine had no effect on male or female fertility.

Tenofovir Alafenamide

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Tenofovir Alafenamide/Emtricitabine. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Alafenamide/Emtricitabine.

Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays. Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peripostnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential and toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

Dolutegravir

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (24 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (27 times the 50 mg twice daily human clinical exposure based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.40 times the 50 mg twice daily human clinical exposure based on AUC). In rabbits, maternal toxicity (decreased food consumption,

scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.40 times the 50 mg twice daily human clinical exposure based on AUC).

In a juvenile toxicity study in rats, dolutegravir administration resulted in two pre-weaning deaths at 75 mg/kg/day. Over the preweaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was ~17-20-fold higher than humans at the recommended pediatric exposure. There were no new target organs identified in juveniles compared to adults. 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 maximum recommended human dose).

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 15 times the human mg/kg equivalent dose (based on a 50 kg human), and 5 times the human mg/m2 equivalent dose for a clinical dose of 50 mg twice daily.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Mannitol
Microcrystalline cellulose
Povidone
Sodium Starch Glycolate
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Purified water

Tablet coating
Polyvinyl Alcohol
Titanium Dioxide
Macrogol
Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

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

6.5. Nature and contents of container

Bottle of 30's, 90's & 180's
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder and manufacturing site addresses

Marketing authorization holder:

Mylan Laboratories Limited
Plot No.564/A/22, Road No.92,
Jubilee Hills, Hyderabad – 500 096,
Telangana, India.
Telephone:0091-40-39258106
Telefax: 0091-40-39258105
E-Mail: Kulbhushan.ganotra@viatris.com

Manufacturing site address:

Mylan Laboratories Limited
Plot No. 11, 12 & 13 Indore Special Economic zone,
Phase –II Sector III,
Pithampur – 454775, Dist.-
Dhar, M.P., India.

8. Marketing authorisation number(s)

CTD9937

9. Date of first authorisation/renewal of the authorisation

09-Dec-2022

10. Date of revision of the text

14-Sep-2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable