SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Spegra

Dolutegravir 50 mg, Emtricitabine 200 mg and Tenofovir alafenamide 25 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Dolutegravir sodium equivalent to Dolutegravir…50mg

Emtricitabine…200mg

Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide….25mg

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications.

Spegra is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) in adults and adolescents (≥12 years of age, and weighing at least 40 kg.

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 40kg

If the patient misses a dose of Spegra within 18 hours of the time it is usually taken, the patient should take Spegra as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Spegra by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Spegra another tablet should be taken.

Elderly
No dose adjustment of Spegra is required in elderly patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment of Spegra is required in adults or adolescents (aged ≥12 years and at least 40 kg body weight with estimated creatinine clearance (CrCl) ≥ 30 mL/min.
Spegra should not be initiated in patients with estimated CrCl < 30 mL/min as there are limited data available regarding the use of this fixed dose combination in this population (see sections 5.1 and 5.2).
Spegra should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment of Spegra is required in patients with hepatic impairment.
The safety and efficacy of Spegra in children younger than 12 years of age, or weighing < 40 kg, have not yet been established. No data are available.

Method of administration
Spegra 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

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.

<u>Patients co-infected with HIV and hepatitis B or C virus</u>
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 Spegra in patients co-infected with HIV-1 and hepatitis C virus (HCV) have not been established. Tenofovir alafenamide is active against hepatitis B virus (HBV), but its clinical efficacy against this virus is under investigation and is not yet fully established.

Discontinuation of Spegra 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 Spegra 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 Spegra 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.

Liver biochemistry 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 biochemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-infected patients.

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.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide 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 postnatally 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 events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present 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.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of 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 include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) 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.

Patients with HIV-1 harbouring mutations.

Spegra should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. Therefore, the same problems may be seen if Spegra is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving Spegra 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.

Patients should be advised that dolutegravir or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV 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).
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.

Co-administration of other medicinal products
The co-administration of Spegra is not recommended with certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), boceprevir, telaprevir, St. John's wort and HIV protease inhibitors (PIs) other than atazanavir, lopinavir and darunavir (see section 4.5).
Spegra should not be administered concomitantly with medicinal products containing tenofovir disoproxil, tenofovir alafenamide emtricitabine, lamivudine or adefovir dipivoxil.
Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminiumcontaining antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epilepticmedicinal products) (see section 4.5).
Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration 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.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.
Spegra should not be administered concomitantly with medicinal products containing tenofovir disoproxil fumarate, lamivudine or adefovir dipivoxil.

Emtricitabine
In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine, and/or the co-administered medicinal product. Medicinal products that decrease renal function may increase concentrations of emtricitabine.

Tenofovir alafenamide
Tenofovir alafenamide is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp activity and BCRP 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 Spegra and development of resistance. Co-administration of Spegra with other medicinal products that inhibit P-gp (e.g., cobicistat, ritonavir, ciclosporin) are expected to increase the absorption and plasma concentration of tenofovir alafenamide. It is not known whether the co-administration of Spegra and xanthine oxidase inhibitors (e.g., febuxostat) would increase systemic exposure to tenofovir.
Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor of CYP3A4 *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.

Other interactions
Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes. Emtricitabine did not inhibit the glucuronidation reaction of a non-specific UGT substrate *in vitro*.
Interactions between the components of fixed-dose combination of dolutegravir, tenofovir alafenamide and emtricitabine and potential co-administered medicinal products are listed in Table 1 (increase is indicated as "↑", decrease as "↓", no change as "↔"). The interactions described are based on studies conducted with fixed-dose combination, or the components of Tenofovir, Emtricitabine as individual agents

and/or in combination, or are potential drug-drug interactions that may occur with fixed-dose combination.

Table 1: Interactions between the individual components of Tenofovir alafenamide, Emtricitabine and Dolutegravir and other medicinal products

Medicinal product by therapeutic areas[1]	**Effects on medicinal product levels. Mean percent change in AUC, C_{max}, C_{min}[2]**	**Recommendation concerning co-administration with Tenofovir alafenamide. Emtricitabine and Dolutegravir**
ANTI-INFECTIVES		
Antifungals		
Ketoconazole Itraconazole Fluconazole Isavuconazole Posaconazole Voriconazole	Interaction not studied with either of the components of this fixed-dose combination. Co-administration of ketoconazole or itraconazole, fluconazole or isavuconazole which are potent P-gp inhibitors, is expected to increase plasma concentrations of tenofovir alafenamide.	This FDC cannot be co-administered with the mentioned list of antifungal agents as the recommended dose of emtricitabine/tenofovir is 200/10 mg once daily, whereas Spegra contains Tenofovir alafenamide 25 mg
Antimycobacterials		
Rifabutin Rifampicin Rifapentine	Interaction not studied with either of the components of this fixed-dose combination. Co-administration of rifampicin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Spegra rifabutin rifampicin, or rifapentine is not recommended.
Anti-hepatitis C virus medicinal products		
Boceprevir	Interaction not studied	Co-administration with boceprevir

Telaprevir	with either of the components of this fixed-dose combination.	or telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of tenofovir alafenamide, therefore co-administration of Spegra with boceprevir or telaprevir is not recommended.
Ledipasvir (90 mg once daily)/ sofosbuvir (400 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (25 mg once daily) [4]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↑ 32% C_{max}: ↔	Spegra cannot be administered with ledipasvir/sofosbovir
Sofosbuvir (400 mg once daily)/ velpatasvir (100 mg once daily), emtricitabine (200 mg once daily)/ tenofovir alafenamide (10 mg once daily)[3]	Sofosbuvir: AUC: ↑ 37% C_{max}: ↔ Sofosbuvir metabolite GS-331007: AUC: ↑ 48% C_{max}: ↔	Spegra cannot be administered with ledipasvir/sofosbovir

	C_{min}: ↑ 58% Velpatasvir: AUC: ↑ 50% C_{max}: ↑ 30% C_{min}: ↑ 60% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir alafenamide: AUC: ↔ C_{max}: ↓ 20%	
ANTIRETROVIRALS		
HIV protease inhibitors		
Atazanavir/cobicistat (300 mg/150 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 75% C_{max}: ↑ 80% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Spegra cannot be administered with atazanavir/cobicistat as the recommended dose of emtricitabine/tenofovir alafenamide is 200/10 mg once daily, whereas Spegra contains tenofovir alafenamide 25 mg.
Atazanavir/ritonavir (300/100 mg once daily), tenofovir alafenamide (10 mg)	Tenofovir alafenamide: AUC: ↑ 91% C_{max}: ↑ 77% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Darunavir/cobicistat (800/150 mg once daily), tenofovir alafenamide (25 mg once daily)[5]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↑ 224% C_{max}: ↑ 216% C_{min}: ↑ 221% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Darunavir/ritonavir (800/100 mg once daily), tenofovir alafenamide	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔	

(10 mg once daily)	Tenofovir: AUC: ↑ 105% C_{max}: ↑ 142% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Lopinavir/ritonavir (800/200 mg once daily), tenofovir alafenamide (10 mg once daily)	Tenofovir alafenamide: AUC: ↑ 47% C_{max}: ↑ 119% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Tipranavir/ritonavir	Interaction not studied with either of the components of fixed-dose combination. Tipranavir/ritonavir results in P-gp induction. Tenofovir alafenamide exposure is expected to decrease when tipranavir/ritonavir is used in combination with fixed-dose combination.	Co-administration with Spegra is not recommended.
Other protease inhibitors	Effect is unknown.	There are no data available to make dosing recommendations for co-administration with other protease inhibitors.
Other HIV antiretrovirals		
Rilpivirine (25 mg once daily), tenofovir alafenamide (25 mg once daily)	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Spegra may be co-administered with Rilpivirine
Efavirenz (600 mg once daily), tenofovir alafenamide (40 mg once daily)[4]	Tenofovir alafenamide: AUC: ↓ 14% C_{max}: ↓ 22%	Spegra may be co-adminstered with Efavirenz.

Maraviroc Nevirapine Raltegravir	Interaction not studied with either of the components of fixed-dose combination. Tenofovir alafenamide exposure is not expected to be affected by maraviroc, nevirapine or raltegravir, nor is it expected to affect the metabolic and excretion pathways relevant to maraviroc, nevirapine or raltegravir.	Spegra may be co-adminstered with Maraviroc, Nevirapine and Raltegravir.
ANTICONVULSANTS		
Oxcarbazepine Phenobarbital Phenytoin	Interaction not studied with either of the components of fixed-dose combination. Co-administration of oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Spegra and oxcarbazepine, phenobarbital or phenytoin is not recommended.
Carbamazepine (titrated from 100 mg to 300 mg twice a day), emtricitabine/tenofovir alafenamide (200 mg/25 mg once daily) [5,6]	Tenofovir alafenamide: AUC: ↓ 55% C_{max}: ↓ 57% Co-administration of carbamazepine, a P-gp inducer, decreases tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of	Co-administration of Spegra and carbamazepine is not recommended.

	resistance.	
ANTIDEPRESSANTS		
Sertraline (50 mg once daily), tenofovir alafenamide (10 mg once daily)[3]	Tenofovir alafenamide: AUC: ↔ C_{max}: ↔ Sertraline: AUC: ↑ 9% C_{max}: ↑ 14%	Spegra may not be administered with Sertraline as there is no data available for interaction between Sertraline and Dolutegravir
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Interaction not studied with either of the components of fixed-dose combination. Co-administration of St. John's wort, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Spegra with St. John's wort is not recommended.
IMMUNOSUPPRESSANTS		
Ciclosporin	Interaction not studied with either of the components of fixed-dose combination. Co-administration of ciclosporin, a potent P-gp inhibitor, is expected to increase plasma concentrations of tenofovir alafenamide.	Spegra cannot be administered with Ciclosporin as the recommended dose of emtricitabine/tenofovir is 200/10 mg once daily, whereas Spegra contains tenofovir alafenamide 25 mg.
ORAL CONTRACEPTIVES		
Norgestimate (0.180/0.215/0.250 mg once daily), ethinylestradiol (0.025 mg once daily), emtricitabine/tenofovir alafenamide (200/25 mg	Norgestromin: AUC: ↔ C_{min}: ↔ C_{max}: ↔ Norgestrel: AUC: ↔ C_{min}: ↔	Spegra may not be co-administered with Norgestimate/ethinylestradiol as there is no data available for interaction of dolutegravir with oral contraceptives.

once daily)[5]	C_{max}: ↔ Ethinylestradiol: AUC: ↔ C_{min}: ↔ $C_{max:}$ ↔	
SEDATIVES/HYPNOTICS		
Orally administered midazolam (2.5 mg once daily), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔	Spegra may be co-administered with Midazolam. .
Intravenously administered midazolam (once daily), tenofovir alafenamide (25 mg once daily)	Midazolam: AUC: ↔ C_{max}: ↔	

[1] When doses are provided, they are the doses used in clinical drug-drug interaction studies.
[2] When data are available from drug-drug interaction studies.
[3] Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination tablet.
[4] Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet.
[5] Study conducted with fixed-dose combination.
[6] Emtricitabine/tenofovir alafenamide was taken with food in this study.

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 (see Table 1). Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration (see Table 1).

The absorption of dolutegravir is reduced by certain anti-acid agents (see Table 1).

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 2 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies of Spegra or its components in pregnant women. There are no or limited 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 1,000 exposed outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine.
Animal studies do not indicate direct or indirect harmful effects of emtricitabine with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. Studies of tenofovir alafenamide in animals have shown no evidence of harmful effects on fertility parameters, pregnancy, or foetal development (see section 5.3).
Spegra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding
It is not known whether tenofovir alafenamide is excreted in human milk. Emtricitabine is excreted in human milk. In animal studies it has been shown that tenofovir is excreted in milk.
There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore, Spegra should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

There are no data on fertility from the use of Spegra in humans. In animal studies there were no effects of emtricitabine and tenofovir alafenamide on mating or fertility parameters (see section 5.3).

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 Spegra 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

Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 4054 HIV-1 infected patients received medicinal products containing emtricitabine, tenofovir alafenamide and Dolutegravir. 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 summary of adverse reactions of Emtricitabine and Tenofovir

The adverse reactions in Table 2 are listed by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 2: Tabulated list of adverse reactions[1]

Frequency	**Adverse reaction**
Immune system disorders	
Uncommon	Hypersensitivity
Uncommon	Immune reconstitution syndrome
Blood and lymphatic system disorders	
Uncommon:	anaemia[2]
Psychiatric disorders	
Common:	abnormal dreams

Common:	Insomnia
Common:	Depression
Nervous system disorders	
Very common:	headache
Common	Dizziness
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea
Common:	vomiting, abdominal pain, flatulence, upper abdominal pain, abdominal discomfort
Hepatobiliary disorders	
Uncommon	Hepatitis
Uncommon:	dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritis
Uncommon:	angioedema[2,3]
Musculoskeletal and connective tissue disorders	
Uncommon:	Arthralgia, myalgia
General disorders and administration site conditions	
Common:	fatigue
Investigations	
Common:	Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) elevations
Common:	Creatine phosphokinase (CPK) elevations

[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 clinical studies 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).

Description of selected adverse reactions

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) 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).

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

Changes in lipid laboratory tests
In studies in treatment-naïve patients, increases from baseline were observed in both the tenofovir alafenamide fumarate and tenofovir disoproxil fumarate containing treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 144. The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 144 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL-cholesterol ratio at Week 144 was 0.2 (-0.3, 0.7) in the E/C/F/TAF group and 0.1 (-0.4, 0.6) in the E/C/F/TDF group ($p = 0.006$ for the difference between treatment groups).
In a study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate to fixed-dose combination while maintaining the third antiretroviral agent (Study GS-US-311-1089), increases from baseline were observed in the fasting lipid parameters total cholesterol, direct LDL cholesterol and triglycerides in the fixed-dose combination arm compared with little change in the emtricitabine/tenofovir disproxil fumarate arm ($p \leq 0.009$ for the difference between groups in changes from baseline). There was little change from baseline in median fasting values for HDL cholesterol and glucose, or in the fasting total cholesterol to HDL cholesterol ratio in either treatment arm at Week 96. None of the changes was considered clinically relevant.

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

Other special populations

Patients with renal impairment
The safety of emtricitabine and tenofovir alafenamide was evaluated through 96 weeks in an open-label clinical study (GS-US-292-0112) in which 248 HIV-1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242)

with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft-Gault method [eGFRCG]: 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function (see section 5.1).

Patients co-infected with HIV and HBV
The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients currently receiving treatment for HIV in an open-label clinical study (GS-US-292-1249). Based on this limited experience, the safety profile of fixed-dose combination in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection (see section 4.4).

Description of selected adverse reactions of Dolutegravir:
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) 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).

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4.9. Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). Treatment of overdose with fixed-dose combination consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.
Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.
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: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations

Mechanism of action
Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV.
Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonoamidate 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 chain-termination.
Tenofovir has activity against HIV-1, HIV-2, and HBV.
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.

Antiviral activity *in vitro*
Emtricitabine and tenofovir alafenamide demonstrated synergistic antiviral activity in cell culture. No antagonism was observed with emtricitabine or tenofovir alafenamide when combined with other antiretroviral agents.

The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013 to 0.64 μM. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

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 EC_{50} 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 (EC_{50} values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

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
In vitro
Reduced susceptibility to emtricitabine is associated with M184V/I mutations in HIV-1 RT.
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.

Cross-resistance in HIV-1 infected, treatment-naïve or virologically suppressed patients
Emtricitabine-resistant viruses with the M184V/I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.
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.

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 data

Clinical efficacy of fixed-dose combination was established from studies conducted with emtricitabine and tenofovir alafenamide when given with integrase inhibitors.

HIV-1 infected, treatment-naïve patients

In a randomised, double-blind, phase 2 trial, in previously untreated adults (aged ≥18 years) with HIV-1 infections (HIV-1 RNA concentrations of at least 1000 copies per mL, CD4 counts of at least 200 cells per µL, estimated glomerular filtration rates of at least 70 mL per min, and HIV-1 genotypes showing sensitivity to emtricitabine and tenofovir were treated with oral once-daily 50 mg dolutegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide for 48 weeks.

At week 24, 31 (93·9%) of 33 in the dolutegravir group. Treatment-emergent adverse events were reported by 22 (67%) of 33 in the dolutegravir plus emtricitabine and tenofovir alafenamide group.

Dolutegravir plus emtricitabine and tenofovir alafenamide showed high efficacy up to 24 weeks. The treatment were well tolerated.

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 3.

Table 3: 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	1%	< 1%	1%	1%

window but on study drug				
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by subgroup				
Age < 50 years ≥ 50 years	716/777 (92%) 84/89 (94%)	680/753 (90%) 104/114 (91%)	647/777 (83%) 82/89 (92%)	602/753 (80%) 92/114 (81%)
Sex Male Female	674/733 (92%) 126/133 (95%)	673/740 (91%) 111/127 (87%)	616/733 (84%) 113/133 (85%)	603/740 (81%) 91/127 (72%)
Race Black Non-black	197/223 (88%) 603/643 (94%)	177/213 (83%) 607/654 (93%)	168/223 (75%) 561/643 (87%)	152/213 (71%) 542/654 (83%)
Baseline viral load ≤ 100,000 copies/mL > 100,000 copies/mL	629/670 (94%) 171/196 (87%)	610/672 (91%) 174/195 (89%)	567/670 (85%) 162/196 (83%)	537/672 (80%) 157/195 (81%)
Baseline CD4+ cell count < 200 cells/mm^3 ≥ 200 cells/mm^3	96/112 (86%) 703/753 (93%)	104/117 (89%) 680/750 (91%)	93/112 (83%) 635/753 (84%)	94/117 (80%) 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^3in 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^3in E/C/F/TDF-treated patients (p = 0.06) at Week 144.

Clinical efficacy of fixed-dose combination 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 4.

Table 4: 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	4%	2%	7%	2%

copies/mL[d]				
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 fixed-dose combination 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 fixed-dose combination (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 5.

Table 5: Virological outcomes of study GS-US-311-1089 at Weeks 48[a] and 96[b]

	Week 48	**Week 96**

	fixed-dose combination containing regimen (n = 333)	**Emtricitabine/tenofovir disoproxil fumarate containing regimen (n = 330)**	**fixed-dose combination 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/mL[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.

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 ($eGFR_{CG}$: 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 96, 88.4% (214/242 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.

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 fixed-dose combination 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%, $p < 0.001$).

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 $eGFR_{CG}$ 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).

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 active-controlled 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% non-white, 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 6.

Table 6 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	267 / 297 (90%)	264 / 295 (89%)	253 / 280 (90%)	238 / 288 (83%)
>100,000	94 / 114 (82%)	87 / 116 (75%)	111 / 134 (83%)	100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)				
<200	43 / 55 (78%)	34 / 50 (68%)	45 / 57 (79%)	48 / 62 (77%)
200 to <350	128 / 144 (89%)	118 / 139 (85%)	143 / 163 (88%)	126 / 159 (79%)
≥350	190 / 212 (90%)	199 / 222 (90%)	176 / 194 (91%)	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	308 / 348 (89%)	305 / 355 (86%)	307 / 347 (88%)	291 / 356 (82%)

Female	53 / 63 (84%)	46 / 56 (82%)	57 / 67 (85%)	47 / 63 (75%)
Race				
White	306 / 346 (88%)	301 / 352 (86%)	255 / 284 (90%)	238 /285 (84%)
African-America/African Heritage/Other	55 / 65 (85%)	50 / 59 (85%)	109 / 130 (84%)	99 / 133 (74%)
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 4 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 non-inferior 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 open-label 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 7.

Table 7 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	186 / 249 (75%)	180 / 254 (71%)
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm^3)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)

200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (72%)
Background Regimen		
Genotypic Susceptibility Score* <2	155 / 216 (72%)	129 / 192 (67%)
Genotypic Susceptibility Score* =2	96 / 138 (70%)	101 / 169 (60%)
Use of DRV in background regimen		
No DRV use	143 / 214 (67%)	126 / 209 (60%)
DRV use with primary PI mutations	58 / 68 (85%)	50 / 75 (67%)
DRV use without primary PI mutations	50 / 72 (69%)	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 multicentre, 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 8.

Table 8 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, Table 9. The overall susceptibility score (OSS) of the optimised background regimen (OBR) was not associated with Week 24 response, nor with the week 48 response.

Table 9 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 Group	**OSS=0**	**OSS=1**	**OSS=2**	**OSS>2**	**Total**	**Total**
No primary IN mutation[1]	2/2 (100%)	15/20 (75%)	19/21 (90%)	9/12 (75%)	45/55 (82%)	38/55 (69%)
Primary mutation other than Q148H/K/R[2]	2/2 (100%)	20/20 (100%)	21/27 (78%)	8/10 (80%)	51/59 (86%)	50/58 (86%)
Q148 + 1 secondary mutation[3]	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 123/186 (66%). 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 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.
The European Medicines Agency has deferred the obligation to submit the results of studies with fixed-dose combination in one or more subsets of the paediatric population in the treatment of HIV-1 infection (see section 4.2 for information on paediatric use).

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.

Table 10 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	84[a]	209[b]
Median Percent Change from Baseline	5%[a]	8%[b]

[a] 22 subjects contributed Week 48 CD4+ cell count data
[b] 21 subjects contributed Week 24 CD4+ cell count data
The European Medicines Agency has deferred the obligation to submit the results of studies with Dolutegravir in paediatric patients aged 4 weeks to below 6 years with HIV infection (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties

Absorption
Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the (mean ± SD) steady state plasma emtricitabine peak concentrations (C_{max}) were 1.8 ± 0.7 μg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 μg•h/mL. The mean steady state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC90 value for anti-HIV-1 activity.
Emtricitabine systemic exposure was unaffected when emtricitabine was administered with food.

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 fixed-dose combination 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%).

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
In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 μg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

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%.

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

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP enzymes. Following administration of [^{14}C]-emtricitabine, complete recovery of the emtricitabine dose was achieved in urine (~86%) and faeces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

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 [^{14}C]-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.

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 P_{450} (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
Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.
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 eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.
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.

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 adults (Table 9).

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.

Table 11: 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)
C_{max} (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)
C_{tau} (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).

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
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.

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.

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.

<u>Polymorphisms in drug metabolising enzymes</u>
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).

<u>Gender</u>
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

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Emtricitabine has demonstrated low carcinogenic potential in mice and rats.

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 fixed-dose combination. 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 fixed-dose combination.
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 peri-postnatal 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 fetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

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 preweanling 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 postweaning 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/m^2 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/m^2 equivalent dose for a clinical dose of 50 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol,

Microcrystalline cellulose,

Sodium starch glycolate,

Povidone K30,

Sodium stearyl Fumarate,

Croscarmellose sodium,

Magnesium stearate,

Opadry II white 85F18422

Contents of Opadry II White 85F18422

Containing Polyvinyl alcohol-part hydrolyzed, Macrogol/PEG, Talc, Titanium dioxide

6.2. Incompatibilities

None known.

6.3. Shelf life

24 Months

6.4. Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86° F).

6.5. Nature and contents of container

30 tablets are packed in HDPE bottle container.

90 tablets are packed in HDPE bottle container

6.6. Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Limited

I.T.B.T. Park, Hinjawadi, Pune - 411057, INDIA

8. MARKETING AUTHORISATION NUMBER(S)

To be assigned

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

10 August 2017