HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
28 May 2014

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TIVICAY 50 mg, film-coated tablet
Bottle of 30 (CIP: 34009 277 146 3 4)

Applicant: VIIV HEALTHCARE SAS

INN	dolutegravir
ATC code (year)	J05AX12 (integrase inhibitor antiviral)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"TIVICAY is indicated in combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV)-infected adults and adolescents above 12 years of age."**

Actual Benefit:	**The actual benefit of TIVICAY in the indication "treatment of Human Immunodeficiency Virus (HIV)-infected adults and adolescents above 12 years of age" is <u>substantial</u> in antiretroviral naïve patients and in experienced patients with prior treatment failure.**
Improvement in Actual Benefit	**<u>In antiretroviral-naïve or experienced patients whose virus does not have integrase inhibitor (INI) resistance mutations</u>:** **The Transparency Committee considers that TIVICAY (dolutegravir) in combination with other antiretrovirals provides a minor improvement in actual benefit (level IV) compared with raltegravir (ISENTRESS) due to having an immunological and virological efficacy that is not inferior to that of raltegravir with a higher genetic barrier to the development of resistance and better ease of use than raltegravir (a single dose versus two daily doses in the case of raltegravir).** **<u>In patients who have no therapeutic options and whose virus is susceptible to dolutegravir</u>:** **The Transparency Committee considers that TIVICAY (dolutegravir), in combination with an optimised background regimen, provides a moderate improvement in actual benefit (level III) in terms of immunological and virological efficacy in therapeutic management.**
Therapeutic use	- **<u>Antiretroviral therapy-naïve patients</u>** **In this population, it is currently recommended to use preferentially two NRTIs combined with an NNRTI (ideally efavirenz, or rilpivirine only in patients with a low viral load ≤ 100,000 copies/ml), or with a PI (darunavir, atazanavir). The currently available INIs (raltegravir or elvitegravir) are not included among the preferred first-line options.** **The incidence of neuropsychiatric disorders in patients treated with efavirenz and the low genetic barrier of NNRTIs (efavirenz and rilpivirine), a single mutation being sufficient to lead to resistance, could encourage preferential use of dolutegravir in place of an NNRTI.** **Compared with other INIs, the ease of use of dolutegravir (a single daily intake) and its higher genetic barrier compared with raltegravir (ISENTRESS) should see its eventual replacement by dolutegravir. The necessity for a booster and the low genetic barrier of elvitegravir [STRIBILD], lower than that of raltegravir and dolutegravir, limits the benefit of this compound.** **On the other hand, dolutegravir loses its advantage of a single daily intake in the case of viruses resistant to INIs (raltegravir, elvitegravir), but susceptible to dolutegravir.** - **<u>Treatment-experienced patients (in virological failure)</u>** **In these circumstances, treatment depends on the virus genotyping resistance.** **In treatment-experienced patients whose virus does not have INI-resistance mutations, dolutegravir should be preferred to raltegravir owing to its greater ease of use and higher genetic barrier. Elvitegravir has not shown any efficacy in these situations and is not recommended.** **On the other hand, it would seem premature, because of a weaker effect on cholesterol, to prefer dolutegravir over a PI (in particular darunavir) in this situation because PIs have a higher genetic barrier. According to the Morlat guideline, the new treatment will preferentially combine an active PI/r (essentially darunavir/r in two daily intakes of 600 mg, more rarely tipranavir/r; the combination of two PIs is not recommended), with two other active ARVs, including dolutegravir.** **Dolutegravir has demonstrated its effectiveness in experienced patients who have no therapeutic options and whose virus is susceptible to dolutegravir, and thus represents in these patients a therapeutic option of choice.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	16 January 2014 (centralised procedure)
Prescribing and dispensing conditions /special status	List I Initial annual hospital prescription. Unrestricted renewal.

ATC Classification	2013	
	J	Antiinfectives for systemic use
	J05	Antivirals for systemic use
	J05A	Direct-acting antivirals
	J05AX	Other antivirals
	J05AX12	Dolutegravir

02 BACKGROUND

TIVICAY (dolutegravir) is an antiretroviral (ARV) medicinal product belonging to the class of integrase inhibitors (INI), having a higher genetic resistance barrier than other ARVs in the class.

Since 14.12.2011, TIVICAY has been available under a temporary authorisation for use by a named patient [ATU nominative in French] for patients infected with HIV in virological failure with an INI-resistant virus. Its use is subject to a Therapeutic Use and Data Gathering Protocol (PUT) validated by the ANSM [French National Agency for Medicines and Health Products Safety] on 24.02.2012. Since 14.12.2011, 91 initial ATU nominative and 175 renewals have been granted by ANSM.
This dossier relates to the application for the inclusion of TIVICAY 50 mg on the list of medicinal products refundable by National Health Insurance and approved for hospital use and various public services.

03 THERAPEUTIC INDICATION

“TIVICAY is indicated in combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV)-infected adults and adolescents above 12 years of age.”

04 DOSAGE

“TIVICAY should be prescribed by physicians experienced in the management of HIV infection.

Posology
Adults

Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class
The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily.
TIVICAY should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to section 4.5 of the SPC.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)
The recommended dose of dolutegravir is 50 mg (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern (see section 5.1 of the SPC).
Co-administration of TIVICAY with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). Please refer to sections 4.4 and 4.5 of the SPC.

Missed doses
If the patient misses a dose of TIVICAY, the patient should take TIVICAY as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Adolescents aged 12 and above
In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily.

Elderly
There are limited data on the use of dolutegravir in patients aged 65 years and older. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2 of the SPC).

Renal impairment
No dosage adjustment is required in patients with mild, moderate, or severe (CrCl <30 ml/min, not on dialysis) renal impairment. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2 of the SPC).

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

Paediatric population
The safety and efficacy of TIVICAY in children aged less than 12 years or weighing less than 40 kg have not yet been established. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for TIVICAY in children and adolescents. Currently available data are described in section 4.8, 5.1 and 5.2 of the SPC, but no recommendation on a posology can be made.

Method of administration
Oral administration.
TIVICAY can be taken with or without food (see section 5.2 of the SPC). In the presence of integrase class resistance, TIVICAY should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations) (see section 5.2 of the SPC)."

05 THERAPEUTIC NEED

HIV infection is a serious, life-threatening pathology.

The aim of antiretroviral treatment, regardless of the situation (first−line, further lines, including after multiple failure), should be to achieve and maintain a plasma viral load of < 50 copies/ml and a CD4 lymphocyte count > 500/mm^3.

Six classes of anti-HIV medicinal products with different action mechanisms are available for the management of HIV-infected patients: nucleoside/tide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), integrase inhibitors (INI), and CCR5 receptor antagonists.

At the present time, therapeutic combinations combining at least three highly active agents are recommended. These treatment regimens can help increase survival, reduce opportunistic infections and HIV infection-related complications, and improve quality of life. First-line triple therapy remains a combination of two NRTIs with a third agent (1 PI or 1 NNRTI). Fusion inhibitors, integrase inhibitors, and CCR5 receptor antagonists are not preferred first-line choices.

In a virological failure situation it is recommended:
- to put together a treatment regimen including, wherever possible, three active medicinal products, based on the treatment history, successive genotypes, and possibly measurements of the plasma concentrations of the antivirals,
- regardless of the failure situation, to regain and maintain a viral load of < 50 copies/ml,
- not to introduce a new treatment comprising only one active medicinal product,
- not to discontinue insufficiently effective ARV treatment, even if seemingly no new treatment option can be envisaged,
- in cases of limited viral replication (VL < 200 copies/ml), as far as possible to correct the causes of virological failure and only change the ARV treatment if viral replication persists, especially if the latter increases and is getting close to the 200 copies/ml threshold, and if the patient is receiving a treatment comprising an NNRTI or an INI,
- in confirmed cases of virological failure (VL > 200 copies/ml), to rapidly modify the ARV treatment by choosing the new treatment during a multidisciplinary consultation meeting involving clinicians, virologists, and pharmacologists.

The latest compounds, whether belonging to new or existing classes, play an important role in a multiple resistance context.

➢ Coverage of therapeutic need

The treatments currently available are effective against virus replication but do not allow its eradication. Their safety and the emergence of long-term resistance remain a matter of concern. Moreover, with ageing of the HIV-infected population, the prevalence of co-morbidities increases, exposing in particular these patients, who are often polymedicated, to drug interactions.

Also, there is a continuing significant need for new antiretrovirals with improved profiles regarding safety, resistance, and drugs interaction.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Proprietary medicinal products belonging to the same therapeutic category – human immunodeficiency virus (HIV) integrase inhibitor (INI) – that have Marketing Authorisation for the treatment of human immunodeficiency virus infection are (cf. Table 1):

- two INI proprietary medicinal products on their own:
  - ISENTRESS (raltegravir)
  - VITEKTA (elvitegravir)
- a fixed-dose combination of one INI, a booster, and two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs):
  - STRIBILD (emtricitabine, cobicistat, elvitegravir, and tenofovir)

Only ISENTRESS is refundable in all its indications (HIV-1 infection in treatment-experienced or naïve patients aged 2 years and above). STRIBILD is refundable only in the treatment of HIV-1 infections in adults aged 18 years and above, naïve of any antiretroviral treatment.
As yet, VITEKTA has not been assessed by the Transparency Committee.

The other treatments recommended for the treatment of HIV infection are as follows (cf. Table 2):

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors (FIs)
- CCR5 receptor antagonists
- Integrase inhibitors (INIs)

At the present time, treatments combining at least 3 highly active agents are recommended as first-line treatments and include 2 NRTIs + a third agent (1 PI or 1 NNRTI):

- 2 NRTIs (tenofovir/emtricitabine) + 1 NNRTI (efavirenz),
- 2 NRTIs (tenofovir/emtricitabine) + 1 NNRTI (rilpivirine),
- 2 NRTIs (abacavir/lamivudine) + 1 NNRTI (efavirenz),
- 2 NRTIs (tenofovir/emtricitabine) + 1 PI/ritonavir (atazanavir/ritonavir or darunavir/ritonavir),
- 2 NRTIs (abacavir/lamivudine) + 1 PI/ritonavir (atazanavir/ritonavir).

These medicinal products all have a substantial actual benefit and are refundable by compulsory Social Security schemes.

06.2 Other health technologies

N/A

◗ Conclusion

The most relevant comparators are:

- **the proprietary medicinal products ISENTRESS (raltegravir) and STRIBILD, both belonging to the same therapeutic category (integrase inhibitors)**
- **other medicinal products in the class of PIs or NNRTIs used as the third agent in tritherapy with 2 NRTIs.**

Table 1: HIV integrase inhibitors (INIs)

Name (INN) Company	Indication	Transparency Committee Opinion
ISENTRESS 400 mg, film-coated tablet, 100 mg, scored chewable tablet and 25 mg, chewable tablet (**raltegravir**) *MSD France*	In combination with other antiretroviral medicinal products, for the treatment of type 1 human immunodeficiency virus (HIV-1) infection in adults, adolescents, and children from the age of 2 years.	➔ **Naïve patients** *Opinion of 03/11/2010* **Substantial actual benefit** **IAB V:** "As superiority has not been demonstrated in terms of immunovirological efficacy compared with available alternative treatments and given the relatively low genetic barrier to the development of resistance (risk of selection of resistant variants) which would limit its use as a first-line treatment in this population, the Committee considers that ISENTRESS does not provide an improvement in actual benefit **(IAB V)** in the management of treatment-naïve adult patients with HIV-1 infection." *Opinion of 06/11/2013* ***(extension of indication to children aged 2 years and over)*** **Substantial actual benefit** **IAB V:** "As superiority has not been demonstrated in terms of immunovirological efficacy compared with available alternative treatments and given the relatively low genetic barrier to the development of resistance (risk of selection of resistant variants) which would limit its use as a first-line treatment in this population, the Committee considers that ISENTRESS (25 mg, 100 mg, and 400 mg tablets), in combination with other antiretrovirals, does not provide an improvement in actual benefit **(IAB V)** in the management of treatment-naïve HIV-1-infected adolescents and children aged 2 years and above." ➔ **Experienced patients** *Opinion of 02/02/2008 and 03/11/2010* **Substantial actual benefit** **IAB III** "Given, on the one hand: - the desirability of having a medicinal product in a new class of antiretrovirals: integrase inhibitors (INIs), - the virological efficacy of ISENTRESS + OT, demonstrated on the reduction in the viral load, which is superior to the investigated comparator (placebo + OT), and on the other hand: - doubts concerning the safety profile of the medicinal product (possible increased risk of cancer and anomalous laboratory results: ALAT, ASAT, CPK), - its potentially low genetic barrier, the Committee considers that ISENTRESS, in combination with an optimised antiretroviral treatment, provides a moderate improvement in actual benefit (IAB III) in terms of virological efficacy in the management of a population restricted to experienced adult patients with a detectable viral load under ongoing antiretroviral treatment who have been confirmed by genotype and phenotype tests to be resistant to at least one nucleoside inhibitor (NRTI), one non-nucleoside inhibitor (NNRTI), and to more than one protease inhibitor (PI)." *Opinion of 06/11/2013* ***(extension of indication to children aged 2 years and above)*** **Substantial actual benefit** **IAB III:** "in combination with an optimised antiretroviral treatment, provide a moderate improvement in actual benefit (IAB III) in terms of immunological and virological efficacy in the management of a population restricted to experienced children and adolescents aged from 2 to < 18 years, with a detectable viral load under ongoing antiretroviral treatment who have been confirmed by genotype and phenotype tests to be resistant to at least one nucleoside inhibitor (NRTI), one non-nucleoside

Name (INN) Company	Indication	Transparency Committee Opinion
		inhibitor (NNI), and to more than one protease inhibitor (PI) and in the absence of mutations diminishing viral susceptibility to this compound."
STRIBILD 150 mg//150 mg/200 mg/245 mg, film-coated tablet (emtricitabine, cobicistat, **elvitegravir** and tenofovir) *GILEAD SCIENCES*	STRIBILD is indicated for the treatment of type 1 human immuno-deficiency virus (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD.	➔ **Naïve patients** *Opinion of 06/11/2013* **Substantial actual benefit** in patients "naïve of any antiretroviral treatment and infected with a strain of HIV-1 without any mutation known to be associated with resistance to any one of the three antiretroviral agents contained in STRIBILD". **IAB V**: "In spite of the simplified dosage regimen, taking into account the absence of any demonstrable superiority in terms of immunological or virological efficacy in comparison with first-line tritherapy, the low genetic barrier to resistance of elvitegravir, and the necessity for increased monitoring of kidney function, and the possible interactions associated with cobicistat, which constitute its current limitations, the Committee considers that STRIBILD does not provide any improvement in actual benefit (IAB V, non-existent) in the management strategy of HIV-1-infected patients naïve of any antiretroviral treatment." ➔ **Experienced patients** *Opinion of 06/11/2013* **Insufficient actual benefit** in experienced patients, including those "infected with a strain of HIV-1 without any known mutation to be associated with resistance to any of the three antiretroviral agents contained in STRIBILD", taking into account the absence of clinical data in this patient population.
VITEKTA 85 mg and 150 mg (**elvitegravir**) *GILEAD SCIENCES*	VITEKTA co-administered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of type 1 human immunodeficiency virus (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir.	*Not marketed to date. Not assessed by the Transparency Committee.*

Table 2: Other antiretrovirals

INN	Proprietary medicinal product Company	Pharmaceutical forms
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)		
Abacavir	ZIAGEN, ViiV Healthcare	Film-coated tablet and oral solution
Didanosine	VIDEX, BMS	Chewable/dispersible tablet, gastro-resistant hard capsule
Emtricitabine	EMTRIVA, Gilead Sciences	Hard capsule and oral solution
Lamivudine	EPIVIR, ViiV Healthcare and generics	Film-coated tablet and oral solution
Stavudine	ZERIT, BMS	Hard capsule and powder for oral solution
Zidovudine	RETROVIR, ViiV Healthcare	Film-coated tablet, hard capsule, oral solution, and solution for injection
Tenofovir disoproxil	VIREAD, Gilead Sciences	Film-coated tablet
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	SUSTIVA, BMS and generics	Tablet, film-coated tablet, hard capsule, and oral solution
Etravirine	INTELENCE, Janssen Cilag	Tablet
Nevirapine	VIRAMUNE, Boehringer Ingelheim and generics	Tablet and oral suspension
Rilpivirine	EDURANT, Janssen Cilag	Film-coated tablet
Protease inhibitors (PIs)		
Atazanavir	REYATAZ, BMS	Hard capsule
Darunavir	PREZISTA, Janssen Cilag	Film-coated tablet and oral suspension
Fosamprenavir	TELZIR, ViiV Healthcare	Film-coated tablet and oral suspension
Indinavir	CRIXIVAN, MSD Chibret	Hard capsule
Lopinavir + ritonavir	KALETRA, ABBVIE	Film-coated tablet and oral solution
Saquinavir	INVIRASE, Roche	Hard capsule, film-coated tablet
Tipranavir	APTIVUS, Boehringer Ingelheim	Soft capsule and oral solution
HIV Protease (PI) or integrase inhibitor booster		
Ritonavir	NORVIR, ABBVIE	Film-coated tablet and oral solution
Cobicistat	TYBOST	Tablet
Fusion inhibitor		
Enfuvirtide	FUZEON, Roche	Powder and solvent for suspension for injection
CCR5 inhibitor		
Maraviroc	CELSENTRI, ViiV Healthcare	Film-coated tablet
Fixed-dose NRTI combinations		
Abacavir + lamivudine	KIVEXA, ViiV Healthcare	Film-coated tablet
Abacavir + lamivudine + zidovudine	TRIZIVIR, ViiV Healthcare	Film-coated tablet
Emtricitabine + tenofovir disoproxil	TRUVADA, Gilead Sciences	Film-coated tablet
Zidovudine + lamivudine	COMBIVIR, ViiV Healthcare and generics	Film-coated tablet
Fixed-dose combinations of 2 NRTIs + 1 NNRTI		
Efavirenz + emtricitabine + tenofovir disoproxil	ATRIPLA, BMS	Film-coated tablet
Rilpivirine + emtricitabine + tenofovir disoproxil	EVIPLERA, Gilead Sciences	Film-coated tablet

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) Marketing Authorisation or restricted population
AUSTRALIA	Yes 01/2014	MA indication
AUSTRIA	Assessment in progress	
BELGIUM	Assessment in progress	
CANADA	Yes Quebec 02/06/2014 Assessment in progress for the other provinces	MA indication
DENMARK	03/03/2014	Restricted to experienced patients
FINLAND	Yes 20/01/2014	MA indication
GERMANY	Yes (15/02/2014)	MA indication
ICELAND	Yes 20/01/2014	MA indication
IRELAND	Yes 01/05/2014	MA indication
ITALY	Assessment in progress	
NETHERLANDS	Assessment in progress	
NORWAY	Yes 01/04/2014	MA indication
SPAIN	Assessment in progress	
SWEDEN	Yes 20/01/2014	MA indication
SWITZERLAND	Yes 01/06/2014	MA indication
UNITED KINGDOM	Yes SMC 15/05/2014 AWMSG, NHSE, assessment in progress	MA indication
UNITED STATES	Yes 08/2013 For 97% of patients included in HIV/AIDS programmes (including Medicaid for most of the principal states)	MA indication

08 ANALYSIS OF AVAILABLE DATA

The dossier comprises six phase III studies conducted in treatment-naïve or experienced patients, as well as one phase I/II study in adolescents aged from 12 years and above, which made it possible to extend the Marketing Authorisation to this paediatric population:

Studies	Study design	Population of HIV-1 patients	Treatments; number of ITT-E patients	Primary efficacy endpoint:
SPRING-2[1,2] *(pivotal)*	Phase III double-blind, randomised, active comparator-controlled, non-inferiority	Naïve adults	- TIVICAY + TRUVADA or KIVEXA , n = 411 - ISENTRESS + TRUVADA or KIVEXA; n = 411	Virological response at 48 weeks
SINGLE[3] *(pivotal)*	Phase III double-blind, randomised, active comparator-controlled, non-inferiority		- TIVICAY + KIVEXA, n = 414 - ATRIPLA, n = 419	
FLAMINGO[4] *(support)*	Phase IIIb open-label, randomised, active comparator-controlled, non-inferiority *(interim report)*		- TIVICAY + TRUVADA or KIVEXA , n = 242 - PREZISTA/NORVIR + TRUVADA or KIVEXA; n = 242	
SAILING[5] *(pivotal)*	Phase III double-blind, randomised, active comparator-controlled, non-inferiority	INI-naïve, experienced adults	- TIVICAY + OT, n = 354 - ISENTRESS + OT; n = 361 *OT: optimised combined treatment at the investigator's choice*	
VIKING-3[6] *(pivotal)*	Phase III, non-comparative	Experienced adults, HIV resistant to INIs and at least two other classes	TIVICAY + treatment failure (7 days) then OT 48 weeks, n = 183	Decrease in the viral load on the 8th day and virological response at 24 weeks
VIKING-4 *(support)*	Phase III double-blind, randomised, placebo-controlled *(interim report)*	Experienced adults, HIV resistant to INIs and at least two other classes	TIVICAY (n = 14) or placebo (n = 16) + treatment failure (7 days) then OT until availability of the product	Decrease in the viral load on the 8th day
P1093 *(pivotal)*	Phase I/II, PK/PD, 6 cohorts of different ages	Cohort I (adolescents aged 12 years and above)	TIVICAY as functional monotherapy for 10 days (+ failed background regimen for patients under treatment) + optimised treatment from 11th day , n = 23	PK/PD parameters

OT: Optimised antiretroviral Therapy

[1] Raffi F, Jaeger H, Quiros-Roldan E et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013; 13: 927-35.

[2] Raffi F, Rachlis A, Stellbrink H-J et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013; 381: 735-743.

[3] Walmsley S L, Antela A, Clumeck N et al. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. N Engl J Med. 2013; 369: 1807-18.

[4] Clotet B, Feinberg J, Van Lunzen J et al. Once-Daily Dolutegravir Is Superior to Darunavir + Ritonavir in Antiretroviral Naïve Adults with HIV-1 Infection: 48 Week Results from the Randomised Study ING114915. Lancet 2014. http://dx.doi.org/10.1016/S0140-6736(14)60084-2.

[5] Cahn P, L Pozniak A L, Mingrone H et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013; 382: 700-08.

[6] Castagna A, Maggiolo F, Penco G et al. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. J Infect Dis. 2014 Feb 23. In press.

In addition, the company presented a network meta-analysis, unpublished, which sought to compare the efficacy and safety of TIVICAY with those of the other three reference agents at treatment initiation in naïve patients: boosted PIs (darunavir/r, lopinavir/r, atazanavir/r), NNRTIs (efavirenz, rilpivirine), and INIs (raltegravir, elvitegravir/cobicistat).

Furthermore, the company provided the following dose-finding and dosage regimen studies that will not be described in detail in this opinion:

- Study ING112276 (SPRING-1):[7]
  Phase I/II study evaluating the various dosages of dolutegravir (DTG) 10, 25, 50 mg versus efavirenz (EFV) 600 mg combined with 2 NRTIs (ABC/3TC or TDF/FTC) lasting 96 weeks in 205 naïve adult patients.
- Study ING112961 (VIKING):[8]
  Phase IIb, non-comparative study evaluating the antiviral activity of monotherapy for 10 days with dolutegravir 50 mg once daily or twice daily in patients with documented resistance to integrase inhibitors.

08.1 Efficacy

8.1.1 Antiviral treatment-naïve adult patients infected with HIV

- **Phase III pivotal studies (SPRING-2 and SINGLE)**

Description of the studies: the methodology of the two studies is described in Table 3.

Table 3: Methodology of the SPRING-2[1] and SINGLE[3] studies

	SPRING-2	SINGLE*
Date and place of study	Started 19/10/2010 and still ongoing at 100 centres: France, Germany, Italy, Spain, United Kingdom, United States, Canada, Russia, Australia. The date of the last observation at week 96 was 30/01/2013.	Started 01/02/2011 and still ongoing at 136 centres: Germany, Belgium, Denmark, Spain, France, Italy, Netherlands, Romania, United Kingdom, United States, Canada, Russia, Australia. The date of the last observation at week 96 was 12/04/2013.
Principal objective and method	Double-blind, randomised (1:1) controlled, non-inferiority study comparing the efficacy and safety over 48 weeks of treatment with:	
	dolutegravir (DTG 50 mg once daily) versus raltegravir (RAL 400 mg twice daily), combined with an optimised treatment with 2 NRTIs: KIVEXA (3TC/ABC) or TRUVADA (TDF/FTC)	dolutegravir (DTG 50 mg once daily) combined with KIVEXA (3TC/ABC) versus ATRIPLA (EFV/FTC/TDF).
	Patients stratified based on: - viral load > or ≤ 100,000 copies/ml - treatment combined with KIVEXA or TRUVADA	Patients stratified based on: - viral load > or ≤ 100,000 copies/ml - number of Ly CD4+ > or ≤ 200 cells/mm^3
Study population	Antiretroviral treatment-naïve adult patients with HIV-1 infection.	
Inclusion criteria	- Patients aged 18 years and above; - Plasma viral load (HIV-1 RNA) ≥ 1000 copies/ml; - Antiretroviral treatment-naïve (≤ 10 days of previous ARV treatment);	
	- HLA-B*5701 test negative for patients receiving abacavir (KIVEXA).	- HLA-B*5701 test negative for all included patients.

[7] Van Lunzen J, Maggiolo F, Arribas JR et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis, 2012; 12: 111-8.

[8] Eron J J, Clotet B, Durant J et al. Safety and Efficacy of Dolutegravir in Treatment-Experienced Subjects With Raltegravir-Resistant HIV Type 1 Infection: 24-Week Results of the VIKING Study. J Infect Dis. 2013; 207: 740-8.

Non-inclusion criteria	- Pregnancy, lactation; - Stage C patient, with the exception of Kaposi's sarcoma skin lesions not requiring systemic treatment or a CD4+ lymphocytes count < 200/mm^3; - Patient with a history of malignant diseases during the 5 years prior to randomisation or with a malignant disease other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or noninvasive resectable squamous cell carcinoma; - Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening, or treatment with radiotherapy, cytotoxic agents, or any immunomodulator within 28 days of screening; - Any proof of primary viral resistance (screening or known resistance); - Any documented grade 4 biological abnormality; - ALAT > 5 × ULN or ALAT > 3 × ULN and bilirubin > 1.5 × ULN (with > 35% conjugated bilirubin); - Creatinine clearance CrCl < 50 ml/min (Cockroft-Gault); - Recent upper/lower gastrointestinal tract bleeding (≤3 months), with the exception of anal or rectal bleeding; - Moderate to severe hepatic failure.
Treatment groups	- TIVICAY (DTG 50 mg once daily) + fixed-dose combination of two NRTIs (KIVEXA or TRUVADA) + ISENTRESS placebo (n = 411); - ISENTRESS (RAL 400 mg twice daily) + fixed-dose combination of two NRTIs (KIVEXA or TRUVADA) + one TIVICAY placebo (n = 411). - TIVICAY 50 mg (once daily) + KIVEXA (once daily) + one ATRIPLA placebo (once daily), n = 414; - ATRIPLA (once daily) + one TIVICAY placebo and one KIVEXA placebo, n = 419.
Course of the study	- Treatment duration: randomised double-blind for week 96 (follow-up visits planned at weeks 2, 4, 8, 12, 16, 24, 32, 40 and 48, then every 12 weeks) - an open-label follow-up phase was planned in the protocol after week 96 of follow-up.
Endpoints	***Primary endpoint*** - Virological response at week 48 (proportion of patients with an HIV-1 RNA viral load < 50 copies/ml), according to the "Snapshot" statistical analysis (analysis corresponding to the last VL value observed between week 44 and 54). ***Secondary endpoints, in particular:*** - Virological response at week 96; - Immunological response (change in the CD4+ count) - Times to virological suppression (SINGLE only). - Safety, resistance.
Calculation of the number of subjects required	It was proposed to include 394 patients in each study group, randomised in a 1:1 ratio in order to establish non-inferiority in terms of the percentage of responders at week 48, with a power of at least 90%, estimating a percentage response of 75%, a non-inferiority limit of 10%, and a one-sided alpha risk of 0.025.
Statistical analysis	Exposed intention-to-treat population (ITT-E): all randomised patients who had received at least one treatment dose; Per protocol population (PP): all randomised patients who had received at least one treatment dose and who had taken part in the study without any major protocol violation (including violation of the inclusion criteria). In the event of non-inferiority is shown in ITT-E population, confirmed by analysis as a PP population, *a test for superiority was prespecified*

*** It should be pointed out that ATRIPLA, the chosen comparator in the SINGLE study, does not have Marketing Authorisation in Europe in the treatment of HIV-1 infection in naïve subjects. Its European Marketing Authorisation is restricted to *"virologically-controlled adult subjects (with a viral load < 50 copies/ml) for more than three months with an antiretroviral combination".* Moreover, the results of this study, which are not readily transferable, will be presented only for information purposes.**

Results

Characteristics of included patients (cf. Appendix Table 10)

In total:

- 827 patients were randomised (1:1) in the SPRING-2 study, 822 of whom received at least one treatment dose and were included in the ITT-E population (dolutegravir group = 411, raltegravir group = 411) and 774 patients in the per protocol population (dolutegravir group = 387, raltegravir group = 387);

- 844 patients were randomised (1:1) in the SINGLE study, 833 of whom received at least one treatment dose and were included in the ITT-E population (dolutegravir group = 414, ATRIPLA group = 419) and 815 patients in the per protocol population (dolutegravir group = 403, ATRIPLA group = 412).
- The baseline demographic and clinical characteristics of patients were comparable in both treatment groups in each of the studies. The median age was 35 to 37 years, with mostly men (about 85%). The median viral load (plasma HIV-1 RNA) was between 4.5 and 4.7 $\log_{10}$ copies/ml (about 70% with a low viral load ≤ 100,000 copies/ml) and the median CD4+ count at baseline was 360 cells/mm^3 in SPRING-2 and 338 cells/mm^3 in SINGLE. The majority of patients (> 80%) were in stage A (asymptomatic) of the infection. Few of the patients (< 10%) were co-infected with HBV or HVC.

Efficacy

In both studies, the non-inferiority of TIVICAY in relation to the comparators was demonstrated by the PP population analysis and confirmed by the ITT-E analysis on the basis of the virological response (viral load < 50 copies/ml at week 48):

- SPRING-2: in combination with KIVEXA or TRUVADA, 90% viral response at week 48 in the TIVICAY group versus 88% in the ISENTRESS group with a difference of +1.6%; 95% CI [-2.7; 5.9] (ITT-E: 88% versus 85%; +2.4% [-2.2; 7.1]);
- SINGLE: 90% virological response at week 48 in the TIVICAY + KIVEXA group versus 81% in the ATRIPLA group with a difference of +8.7% 95% CI [+3.9; +13.4] (ITT-E: 88% versus 81%; +7.4% [+2.5; +12.3]).

Non-inferiority was confirmed with the results in the subgroups "viral load ≤ or > 100,000 copies/ml", "combined treatment TRUVADA or KIVEXA" in the SPRING-2 study, and "CD4+ initially ≤ or > 200 cells/mm^3" in the SINGLE study.

Superiority study provided for in the protocol in the event of non-inferiority in the ITT and PP analyses:

- The superiority of TIVICAY over ISENTRESS was not demonstrated (lower limit of 95% CI < 0).
- The superiority of the TIVICAY and KIVEXA combination over ATRIPLA was demonstrated (lower limit of 95% CI > 0).

Table 4: Results at week 48 and 96 of the SPRING-2 and SINGLE studies (ITT-E and PP population)

	SPRING-2		SINGLE	
n (%)	**TIVICAY (n = 411)**	**ISENTRESS (n = 411)**	**TIVICAY + KIVEXA (n = 414)**	**ATRIPLA (n = 419)**
Virological response at week 48 (HIV RNA < 50 copies/ml) *n (%); adjusted difference (DTG-comparator) [95% CI]*				
Total PP populations	**348/387 (90%)**	**342/387 (88%)**	**362/403 (90%)**	**335/412 (81%)**
	+ 1.6% [-2.7; 5.9]		**+8.7% [+3.9; +13.4]**	
Total ITT-E populations	**361/411 (88%)**	**351/411 (85%)**	**364/414 (88%)**	**338/419 (81%)**
	+2.5% [-2.2; 7.1]		**+7.4% [2.5; 12.3]**	
initial viral load ≤ 100,000 copies/ml	267/297 (90%)	264/295 (89%)	253/280 (90%)	238/288 (83%)
	+ 0.4% [-4.5; 5.3]		+7.7% [2.1; 13.3%]	
initial viral load > 100,000 copies/ml	94/114 (82%)	87/116 (75%)	111/134 (83%)	100/131 (76%)
	+7.5% [-3.1; 18.0]		+6.5% [-3.2; 16.2]	
KIVEXA associated. treatment (ABC/3TC)	145/169 (86%)	142/164 (87%)	-	
	-0.8 [-8.2; 6.6]			
TRUVADA associated treatment (TDF/FTC)	216/242 (89%)	209/247 (85%)		
	+4.6% [-1.3; 10.6]			
initial CD4+ count ≤ 200 cells/mm^3	-		45/57 (79%)	48/62 (77%)
			+1.5 [-13.3; 16.4]	
initial CD4+ count > 200 cells/mm^3			319/357 (89%)	290/357 (81%)
			+8.1 [3.0; 13.3]	
Virological failure at week 48 (virological non response)	20/411 (5%)	31/411 (8%)	29/414 (7%)	55/419 (13%)
Virological response at week 96 (HIV RNA < 50 copies/ml) *n (%); DTG-comparator [95% CI]*				
Total ITT-E populations	332/411 (81%)	314/411 (76%)	332/411 (80%)	303/419 (72%)
	+4.4 [-1.2; 10.0]		+ 8.0 [2.3; 13.8]	
Virological failure at week 96 (virological non response)	22/411 (5%)	43/411 (10%)	31/411 (7%)	33/419 (8%)
Immunological response (increased CD4+ count (cells/mm^3) at week 96) *median (Q1; Q2)*				
*at **week** 48*	+ 229.5 (128.0; 338.0)	+ 230.0 (139.0; 354.0)	+ 246.0* (150.0; 352.0)	+ 187.0* (107.0; 304.0)
*at **week** 96*	+ 276.0 (159.0; 402.0)	+ 264.0 (155.0; 396.0)	+ 299.0** (199.0; 427.0)	+ 264.5** (157.5; 380.5)

*p < 0.001; **p < 0.004

The time to virological suppression (HIV RNA < 50 copies/ml) was not evaluated in the SPRING-2 study. In the SINGLE study, it was shorter in patients treated with TIVICAY + KIVEXA, median of 28 days, compared with the group treated with ATRIPLA, median of 84 days (HR = 2.32; 95% CI [2.00; 2.68], p < 0.0001).

- **Phase IIIb support studies (FLAMINGO)**

Study design: open-label, randomised, controlled, non-inferiority study evaluating the efficacy and safety of dolutegravir (DTG 50 mg once daily) versus darunavir/ritonavir (PREZISTA/NORVIR), in combination with 2 NRTIs (KIVEXA or TRUVADA) during 96 weeks of treatment.

Inclusion criteria: antiretroviral treatment-naïve adult patients (≥ 18 years) infected with HIV-1 with a baseline plasma viral load ≥ 1000 copies/ml and a negative HLA B*5701 test for patients receiving KIVEXA.

Primary efficacy endpoint: virological response at week 48 (proportion of patients with an HIV-1 RNA viral load < 50 copies/ml), according to the "Snapshot" statistical analysis. In this trial, the non-inferiority limit was 12%.

Treatment groups

- *Dolutegravir group:* TIVICAY (DTG 50 mg once daily + fixed-dose combination of two NRTIs (KIVEXA or TRUVADA; once daily) (n = 242);
- *Darunavir/r group:* PREZISTA (darunavir 400 mg twice daily) + NORVIR (ritonavir 100 mg once daily) + fixed-dose combination of two NRTIs (KIVEXA or TRUVADA; once daily (n = 242).

Results (cf. Table 5)

A total of 488 patients were randomised (1:1) in the FLAMINGO study, 484 of whom received at least one treatment dose and were included in the mITT-E population (dolutegravir group = 242, darunavir/r group = 242) and 472 patients in the per protocol population at week 48 (dolutegravir group = 237, darunavir/r group = 235). The mITT-E population is defined by all randomised patients who had received at least one treatment dose with the exception of one randomised patient in the dolutegravir group included by a centre withdrawn from the study for failure to adhere to good clinical practice.

The demographic and clinical characteristics of the patients were comparable with those presented in the SINGLE and SPRING-2 studies: median age of 34 years, mostly men (85%), median viral load of 4.48 $\log_{10}$ copies/ml (viral load ≤ 100,000 copies/ml for 75% of the patients), and a median CD4+ cells count of 400 /mm^3.

At week 48, the non-inferiority of TIVICAY compared with PREZISTA/r was demonstrated in the PP population (91% DTG group versus 84% darunavir/r group; difference +7.4% [1.4; 13.3]), and confirmed in the mITT-E population (90% versus 83%; +7.1% [0.9; 13.2]). The superiority of TIVICAY in comparison with PREZISTA/r (as per the protocol) was demonstrated (lower limit of the 95% CI of the difference > 0).

The time to virological suppression (HIV RNA < 50 copies/ml) was shorter in patients treated with TIVICAY with a median of 28 days compared with the group treated with PREZISTA, median of 85 days (HR = 3.72; 95% CI [3.05; 4.55], p < 0.001).

Table 5: Results at week 48 FLAMINGO (mITT-E population)

	FLAMINGO *Interim report at week 48*		
n (%)	**TIVICAY (n = 242)**	**PREZISTA/r (n = 242)**	**Difference [95% CI]**
Virological response at week 48 (HIV RNA < 50 copies/ml) *n (%); adjusted difference [95% CI]*			
Total PP populations	**216/237 (91%)**	**197/235 (84%)**	**+7.4 [1.4; 13.3)**
Total mITT-E populations	**217/242 (90%)**	**200/242 (83%)**	**+7.1% [0.9; 13.2]**
initial viral load ≤ 100,000 copies/ml	160/181 (88%)	157/181 (87%)	+1.7% [-5.1; 8.5]
initial viral load > 100,000 copies/ml	57/61 (93%)	43/61 (70%)	+23.0% [9.9; 36.0]
KIVEXA associated treatment (ABC/3TC)	71/79 (90%)	68/80 (85%)	+4.9% [-5.4; 15.1]
TRUVADA associated treatment (TDF/FTC)	146/163 (90%)	132/162 (81%)	+8.1% [0.5; 15.7]
Virological failure at week 48 (virological non response)	15/242 (6%)	18/242 (7%)	-

8.1.2 Experienced adult patients infected with HIV

➢ **Phase III pivotal study, experienced INI-naïve patients (SAILING)**

	SAILING SAILING, Cahn P. et al (2013)
Date and place of study	Begun on 26 October 2010 and still ongoing in 156 centres: Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Greece, Hungary, Italy, Mexico, Netherlands, Romania, Russia, South Africa, Spain, Taiwan, United Kingdom, United States. The date of the last observation at week 48 was reached on 04/02/2013.
Principal objective and method	Double-blind, randomised (1:1) controlled, non-inferiority study comparing the efficacy and safety over 48 weeks of treatment with dolutegravir (DTG 50 mg once daily) versus raltegravir (RAL 400 mg twice daily) combined with an optimised treatment. Patients stratified based on: - viral load > or ≤ 50,000 copies/ml; - use of darunavir/r with or without primary resistance to protease inhibitors.
Study population	Experienced adult HIV-1 infected patients but naive for integrase inhibitor treatment .
Inclusion criteria	- Antiretroviral-experienced patients aged 18 years or above; - Documented viral resistance to at least two different classes of ARVs (resistance test) or known resistance in patients naïve to ARV treatment for over one month; - INI-naïve patients (no exposure to raltegravir, elvitegravir, dolutegravir) - Viral load ≥ 400 copies/ml at two assessments except if > 1000 copies/ml at selection.
Non-inclusion criteria	- Pregnancy, lactation; - Moderate to severe hepatic failure; - No fully active antiviral agent available to establish the background regimen (detected at the time of the selection resistance test); - Absence of baseline genotype/phenotype/or virus tropism data; - Stage C patient, with the exception of Kaposi's sarcoma not requiring systemic treatment or a CD4+ lymphocyte count < 200/mm^3; - Recent upper/lower gastrointestinal tract bleeding (≤ 3 months), with the exception of anal or rectal bleeding; - Patient with a history of malignant diseases during the 5 years prior to randomisation or with a malignant disease other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resectable noninvasive squamous cell carcinoma; - Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening, or treatment with radiotherapy, cytotoxic agents, or any immunomodulator within 28 days of screening. - Any documented grade 4 biological abnormality; - ALAT > 5 × ULN or ALAT > 3 × ULN and bilirubin > 1.5 × ULN (with > 35% conjugated bilirubin).
Treatment groups	- TIVICAY (DTG 50 mg once daily) + OT + ISENTRESS placebo (n = 357); - ISENTRESS (RAL 400 mg twice daily) + OT + TIVICAY placebo (n = 362). OT: optimised background regimen consisting of a first fully active ARV and not more than one other ARV (whether active or not). The number of patients treated with PREZISTA/r not presenting any resistance mutation to PIs was deliberately kept to 170 patients in order to be able to observe a virological response attributable exclusively to TIVICAY and not to the background treatment containing PREZISTA/r.
Course of the study	- Treatment duration: randomised, double-blind for 48 weeks (follow-up visits planned at week 2, 4, 8, 12, 16, 24, 32, 40 and 48, then every 12 weeks); - followed by an open-label phase.
Endpoints	***Primary endpoint*** - Virological response at week 48 (proportion of patients with an HIV-1 RNA viral load < 50 copies/ml), according to the "Snapshot" statistical analysis (analysis corresponding to the last VL value observed between weeks 44 and 54). ***Secondary endpoints, in particular:*** - Virological response at week 24; - Tolerability, clinical and biological safety, and immunological response; - Profile of genotypic resistance to virological failure.
Calculation of the number of subjects required	It was proposed to include 344 patients in each treatment group, randomised in a 1:1 ratio in order to establish non-inferiority in terms of the percentage of responders at week 48, with a power of at least 90%, estimating a percentage response of 65%, a non-inferiority limit of 12%, and a one-sided alpha risk of 0.025.

	SAILING SAILING, Cahn P. et al (2013)
Statistical analysis	Exposed intention-to-treat population (mITT-E): all randomised patients who had received at least one treatment dose, with the exclusion of four patients included by one centre (failure to adhere to good clinical practice); Per protocol population (PP): same as SPRING-2 In the event of non-inferiority in the mITT-E and PP population is shown, a test for superiority was prespecified.

Results

Characteristics of included patients (cf. Appendix Table 11)
A total of 724 patients were randomised (1:1) in the SAILING study, 715 of whom received at least one treatment dose and were included in the mITT-E population (dolutegravir group = 354, raltegravir/r group = 361) and 665 patients in the per protocol population at week 48 (dolutegravir group = 325, darunavir/r group = 340). The mITT-E population is defined by all randomised patients who had received at least one treatment dose with the exception of four randomised patients (three in the dolutegravir group and one in the raltegravir group) included by a centre withdrawn from the study for failure to adhere to good clinical practice.

The baseline clinical and demographic characteristics of patients were comparable in both treatment groups. The median age was 42 to 43 years, with mostly men (about 70%). At baseline, almost 70% of patients with a viral load ≤ 50,000 copies/ml and a median CD4+ count (about 200 cells/mm^3) were comparable in the two treatment groups. Almost half the patients were at the AIDS stage of the infection. Almost half the included patients were resistant to at least three classes of ARVs (46% in the DTG group and 50% in the RAL group). The optimised treatments (OTs) received during the study were similar in both groups. The majority of patients received a protease inhibitor combined with ritonavir: darunavir/r + tenofovir (19%), lopinavir/r + tenofovir (11%), darunavir/r + etravirine (10%), lopinavir/r alone (10%), atazanavir/r + tenofovir (10%), darunavir/r + maraviroc (6%).

Efficacy (cf. Table 6):
As regards the primary efficacy endpoint (viral load < 50 copies/ml at week 48), the non-inferiority of TIVICAY versus ISENTRESS was demonstrated in the PP population (73% DTG group versus 66% RAL group; difference +7.5%, 95% CI [0.6; 14.3]), and confirmed by analysis in the mITT-E population (71% versus 64%; +7.4% [0.7; 14.2]). The superiority of TIVICAY over ISENTRESS was demonstrated by the superiority analysis, as provided for by the protocol (lower limit of the 95% CI of the difference > 0).

The immunological response was comparable in both groups, with an increase of the CD4+ cells count of 144 /mm^3 in the DTG group versus 137 /mm^3 in the RAL group.

Table 6: SAILING results at week 48 (mITT-E population)

	SAILING		
	TIVICAY (n = 354)	**ISENTRESS (n = 361)**	**Difference [95% CI]**
Virological response at week 48 (HIV RNA < 50 copies/ml) *n/N (%); % difference [95% CI]*			
Total PP populations	***238/325 (73%)***	***225/340 (66%)***	***+7.5% [0.6; 14.3]***
Total mITT-E populations	***251/354 (71%)***	***230/361 (64%)***	***+7.4% [0.7; 14.2]***
initial viral load ≤ 50,000 copies/ml	*186/249 (75%)*	*180/254 (71%)*	*+3.8 [-3.9; 11.6]*
initial viral load > 50,000 copies/ml	*65/105 (62%)*	*50/107 (47%)*	*+15.2 [1.9; 28.4]*
Virological failure week at 48	*71/354 (20%)*	*100/361 (28%)*	-
Immunological response *(cells/mm^3)*			
CD4+ increase at week 48 *median (Q1; Q2)*	*+144 (73; 242)*	*+137 (67; 224)*	**-**
Associated background regimen			
PSS score < 2*	*70/104 (67)*	*61/94 (65)*	*+2.4 [-10.8; 15.6]*
with DRV/r without primary mutation to PIs	*50/72 (69)*	*54/77 (70)*	*-0.7 [-15.4; 14.1]*
without DRV/r or with DRV/r, with primary mutation to PIs	*201/282 (71)*	*176/284 (62)*	*+9.3 [1.6; 17.0]*

*PSS score: defined as the total number of ARVs in the background regimen to which the patient's viral strain has shown phenotypic susceptibility (based on a phenotypic resistance test).

- **Phase III pivotal studies (VIKING-3)**

Study design: non-comparative study evaluating the antiviral activity and safety of TIVICAY (DTG 50 mg twice daily) in experienced adult patients whose prior treatment including an integrase inhibitor had failed. Phase 1: addition for 7 days of TIVICAY to the failed ARV treatment. Phase 2: combination of TIVICAY with an optimised background regimen comprising at least one fully active agent, up to 48 weeks.

Inclusion criteria: experienced adult patients (≥ 18 years), with documented resistance to raltegravir or elvitegravir, a viral load > 500 copies/ml, and able to receive at least one fully active agent from day 8.

Co-primary endpoints:
- mean variation in the viral load between baseline and the Day 8
- proportion of patients with a viral load < 50 copies/ml at week 24 (virological response).

Results (cf. Table 7)

A total of 183 patients were included and received at least one dose of dolutegravir (ITT-E). The median age was 48 years and the patients were predominantly male (77%), 67% (122/183) had a viral load < 50,000 copies/ml, 79% (144/183) had CD4+ cells count < 350 /mm^3. The majority of patients were at an advanced stage of the disease (56% at the AIDS stage). HIV-HCV coinfection was described in 26 patients (14%).

- Data at Day 8: a decrease in the viral load was observed with TIVICAY combined with the failed ARV treatment for 7 days: a mean of -1.43 $\log_{10}$ copies/ml in the ITT-E population on the 8th day 95% CI [-1.52; -1.34].
- Data at Week 24: virological response was achieved in 72 patients (63%). This percentage response was variable, in cases of primary mutation to INIs and according to the category of resistance documented.

The antiviral activity of dolutegravir was less great in patients with a Q148 resistance profile to INIs than in patients with a non-Q148 resistance profile (including primary mutations N155H, Y143C/H/R).

Table 7: VIKING-3 (mITT-E) results at week 24

VIKING-3		
	TIVICAY (mITT-E n = 183)	
	Virological response (week 24) *n/N (%)*	***variation in the viral load on Day 8 (log_{10} c/ml)*** *mean (SD)*
mITT-E population	*126/183 (69%)*	***-1.43 (0.61)***
Primary mutation detected at inclusion	*79/123 (64%)*	*-1.34 (0.62)*
Primary mutation not detected at inclusion	*47/60 (78%)*	*-1.62 (0.55)*
non-Q148	*100/126 (79%)*	*-1.59 (0.51)*
Q148 + 1 secondary mutation	*21/36 (58%)*	*-1.15 (0.54)*
Q148 + ≥ 2 secondary mutations	*5/21 (24%)*	*-0.92 (0.81)*

- **Phase III pivotal studies (VIKING-4)** *(interim study report on the 8th day)*

Study design: randomised, double-blind, placebo-controlled study evaluating the antiviral activity and safety of TIVICAY (DTG 50 mg twice daily) in experienced adult patients whose prior virological treatment including an integrase inhibitor had failed. Randomised Phase I: addition for 7 days of TIVICAY to the failed ARV treatment. Open-label Phase II: combination of TIVICAY with an optimised background regimen comprising at least one fully active agent.

Inclusion criteria: experienced adult patients (≥ 18 years), with documented resistance to raltegravir or elvitegravir, a viral load > 1000 copies/ml, and able to receive at least one fully active agent from the Day 8.

Primary endpoint: mean variation in the viral load between baseline and the Day 8.

Calculation of the number of subjects required: assuming a difference in the variation in the mean viral load on the Day 8 between the TIVICAY group and the placebo group of 1 log_{10} copies/ml (standard deviation = 0.8), the inclusion of 15 subjects per group gives a power of 91% (α 5%).

Results

The characteristics of the included patients were comparable in the two groups. The median age of the 30 included patients was 49 years (from 19 to 66 years); 80% of the patients were male. The majority of patients were in AIDS category C according to the CDC classification system (19/30, 63%) with a median baseline viral load of 4.42 (log_{10} copies/ml) and a median CD4+ value of 160 cells/mm^3. The proportion of patients with a baseline viral load > 50,000 copies/ml was greater in the placebo group (6/16, 28%) than in the TIVICAY group (2/14, 14%).

On the Day 8, the mean viral load fell by -1.06 log_{10} copies/ml in the TIVICAY group versus an increase of +0.10 log_{10} copies/ml in the placebo group (difference -1.16; 95% CI [-1.52; -0.80]; $p < 0.001$).

Analysis of the response on the Day 8 confirmed the difference in virological response depending on the baseline INI resistance profiles demonstrated in the VIKING-3 study: there is less antiviral activity in patients with a Q148 resistance profile to INIs + ≥ 2 secondary mutations.

Table 8: Results on the 8th day (VIKING-4 study)

VIKING-4					
	TIVICAY (n = 14)		Placebo (n = 16)		
	n	**variation in the viral load on the day 8 (log_{10} copies/ml)** mean (SD)	**n**	**variation in the viral load on the day 8 (log_{10} copies/ml)** mean (SD)	**Difference 95% CI, p**
ITT-E population	**14**	**-1.06 (0.168)**	**16**	**0.10 (0.183)**	**-1.16 [-1.52; -0.80] p < 0.001**
Q148 + 1 secondary mutation	5	-1.07 (0.352)	5	-0.03 (0.194)	-
Q148 + ≥ 2 secondary mutations	4	-0.64 (0.809)	1	+0.09	-
N155	2	-1.13 (0.971)	4	0.11 (0.359)	-
Y143	2	-1.74 (0.949)	4	-0.01 (0.101)	-
≥ 2 primary mutations	1	-1.37	1	-0.17	-

8.1.3 HIV-infected adolescent patients aged > 12 years

- **Phase I/II studies (P1093)** *(interim analysis)*

In accordance with the guidelines on the clinical development of medicinal products intended for the treatment of HIV,[9] if exposure to the medicinal product in adults and children is similar and is assumed to have the same efficacy, only the pharmacokinetic data may be used for extrapolating to children the efficacy data observed in adults.

Study design: Phase I/II, non-comparative, multicentre, dose-finding study conducted in infants, children, and adolescents aged from 6 weeks to 18 years. Six cohorts of patients were envisaged: adolescents ≥ 12 years and < 18 years (Cohort I, adult tablet), children ≥ 6 years and < 12 years (Cohort IIA, adult tablet), children ≥ 6 years and < 12 years (Cohort IIB, paediatric formulation), children ≥ 2 years and < 6 years (paediatric formulation, Cohort III), children ≥ 6 months and < 2 years (Cohort IV, paediatric formulation), infants ≥ 6 weeks and < 6 months (Cohort V, paediatric formulation). This study is still ongoing and only the results for Cohort I are presented here.

Results:

The interim analysis covers only Cohort I up to the 24th week. A total of 23 patients were included. By week 24, no patients had withdrawn the study.

The median age of the patients was 15 years (from 12 to 17 years); 18 girls and 5 boys were included. At baseline, the median viral load was 4.3 log_{10} copies/ml, the median CD4+ cells count was 466 cells/mm^3, and 9 patients were in the AIDS category.

At 24 weeks, 16 out of 23 adolescents (70%) treated with TIVICAY once daily (35 mg: n = 4, 50 mg: n = 19) + optimised background regimen had a viral load < 50 copies/ml (82%, i.e. 19/23 had a viral load < 400 copies/ml). Four subjects were in virological failure, none having had INI resistance at the time of virological failure.

The geometric mean of the AUC_{24} and of C_{24h} in the whole of cohort I at stage I (intensive pk, n = 10) were 46 µg*h/ml and 0.902 µg/ml, respectively. These values were within the pre-set pharmacokinetic target with an exposure of 1 mg/kg of dolutegravir (AUC_{24} 37-67 µg*h/ml and

[9] Guideline on the clinical development of medicinal products for treatment of HIV infection (EMEA/CPMP/EWP/633/02).

C_{24h} 0.770-0.226) in children from 12 to 18 weighing at least 40 kg receiving TIVICAY 50 mg once daily.

The pharmacokinetics of dolutegravir has shown that the oral dose of 50 mg of TIVICAY once daily, in children aged from 12 to 18 years, could result in an exposure comparable with that observed in adults after receiving a dose of 50 mg of dolutegravir orally once daily.

08.2 Resistance data

- **Data from clinical studies**

Among patients in virological failure and included in the resistance analysis:
- at week 96, no patients (0/22) developed at least one resistance mutation in the TIVICAY group, versus 5/29 (or 17%) in the ISENTRESS group (SPRING-2);
- at week 96, no patients (0/18) developed at least one resistance mutation in the TIVICAY group, versus 5/17 (or 29%) in the ATRIPLA group (SINGLE);
- at week 48, no patients (0/2 in each group) developed at least one resistance mutation in the TIVICAY and PREZISTA/r groups (FLAMINGO).

In experienced but protease inhibitor-naïve adult patients (SAILING), INI mutations were discovered in 4 patients (or 1%) in the dolutegravir group versus 17 (or 5%) patients in the raltegravir group.

In the presence of resistance to the INI class (VIKING-3) and in virological failure patients, 15 had viral strains with resistance mutations that appeared under treatment, 4 of which had a Q148 profile on failure. The emergence of resistance to dolutegravir on treatment was observed predominantly in patients with a history of Q148 mutation (baseline or historic).

- **SPC data**

"*Resistance in vitro*

Serial passage was used to study resistance evolution *in vitro*. When using the lab-strain HIV III during passage over 112 days, selected mutations 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 (FC3) and G193E (also FC3) were selected. The E92Q mutation was 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 ARV experienced, INI naïve 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 (FC10), 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 to 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 (FC1), a variety of secondary mutations were seen with a significant 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 analysed for susceptibility to dolutegravir. Dolutegravir had an FC < 10 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 = 876 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 31 patients with protocol defined virological failure (PDVF) through Week 24 and with paired genotypes (all treated with dolutegravir 50 mg twice daily + optimised background agents): L74L/M (n = 1), E92Q (n = 2), T97A (n = 8), E138K/A (n = 7), G140S (n = 2), Y143H (n = 1), S147G (n = 1), Q148H/K/R (n = 4), N155H (n = 1), and E157E/Q (n = 1). Treatment emergent dolutegravir resistance typically appeared in patients with a history of the Q148-mutation (baseline or historic)."

08.3 Safety/Adverse effects

8.3.1 Data from clinical studies

- **Safety analysis population** *(cf. Table 9)*

The safety data presented in this dossier come from the analysis of patients included in the safety analyses in Phase III trials (SPRING-2, SINGLE, FLAMINGO, SAILING, VIKING-3, and VIKING-4). A total of 1067 antiretroviral treatment-naïve patients and 554 experienced patients were taken into account.

Table 9: Safety analysis population

	SPRING-2 Week 96	SINGLE Week 96	FLAMINGO Week 48	SAILING Week 48	VIKING-3 Week 24
TIVICAY 50 mg	**Once daily**	**Once daily**	**Once daily**	**Once daily**	**Twice daily**
Patients analysed for safety	411	414	242	357	183
Treatment discontinuations %	15%	17%	7%	16%	15%
Treatment discontinuations due to an AE	2%	3%	2%	2%	3%
AEs deemed to be treatment-related, all grades, %	30%	44%	33%	20%	25%
Treatment-related AEs, Grade 3 or 4, %	1%	2%	1%	2%	3%
Serious AEs deemed to be treatment-related, %	< 1%	< 1%	< 1%	< 1%	1%

- **Principal types of adverse events** *(cf.* ***Table 10)***

In the group of patients who had received at least one treatment dose (ITT-E), the frequency of adverse events was 87% in naïve patients and 78% in experienced patients. The most common adverse events were:

- Naïve patients: diarrhoea (17%), nausea (15%), headache (15%), nasopharyngitis (14%), and insomnia (10%);
- Experienced patients: diarrhoea (17%), headache (9%), nausea (9%), and upper respiratory tract infections (8%).

In relation to the comparators:

- The safety profiles of the two integrase inhibitors, dolutegravir (TIVICAY) and raltegravir (ISENTRESS) were similar (SPRING-2, SAILING).
- The dolutegravir dosage used (50 mg twice daily) in experienced and INI-resistant patients (VIKING-3 and -4) did not lead to any change in the safety profile relative to that observed in experienced but INI-naïve patients treated with dolutegravir at the dose of 1 tablet of 50 mg daily (SAILING).
- The frequency of adverse events was generally similar in patients treated with TIVICAY in combination with KIVEXA and those treated with ATRIPLA, with the exception of vertigo (10% versus 37%), rash (5% versus 14%), and abnormal dreams (7% versus 17%), which were more frequent in patients treated with ATRIPLA (SINGLE).

- **Adverse events considered to be treatment-related**

The incidence of adverse events considered to be treatment-related was:

- comparable in the TIVICAY and raltegravir groups in the SPRING-2 study (30% TIVICAY versus 29% ISENTRESS) and SAILING study (20% TIVICAY versus 23% ISENTRESS); and of the order of 25% in patients treated with TIVICAY twice daily in the VIKING-3 study;
- lower with TIVICAY + KIVEXA than with ATRIPLA in the SINGLE study (44% versus 67%). Vertigo (7% versus 33%) and abnormal dreams (7% versus 16%) were less common in the TIVICAY + KIVEXA group compared with the ATRIPLA group;
- lower with TIVICAY than with PREZISTA/r in the FLAMINGO study (33% versus 48%), including diarrhoea (9% versus 23%).

The incidence of adverse event-related treatment discontinuations was low (2 to 3%) in patients treated with TIVICAY and lower than its comparators:

- TIVICAY versus ISENTRESS: 2% versus 2% RAL (SPRING-2 in naïve patients at week 96), 2% versus 4% (SAILING in experienced patients at week 48);
- TIVICAY versus PREZISTA/r: 2% versus 4% (FLAMINGO in naïve patients at week 48)
- TIVICAY versus ATRIPLA: 3% versus 12% (SINGLE in naïve patients at week 96)

- **Serious adverse events considered to be treatment-related**

The incidence was low in all trials (< 1%) with a total of 9 cases: 2 hypersensitivity reactions, 2 cases of hepatotoxicity, 1 arrhythmia, 1 attempted suicide, 1 myositis associated with acute renal failure, 1 grade 3 pruritus associated with grade 2 rash, 1 grade 3 skin eruption associated with grade 3 hyperbilirubinaemia, and grade 2 elevated ALAT.

- **Deaths:** 9 deaths were reported during the Phase III studies, 3 of them in patients who had been receiving TIVICAY: 1 homicide, 1 grade 4 progressive multifocal leukoencephalitis, and 1 death of cardiovascular origin. According to the EPAR, 16 deaths were declared in patients treated with dolutegravir (taking into account trials of every phase, compassionate use, and temporary use programmes).

No death was considered to be related to treatment with TIVICAY.

Table 10: Incidence of AEs occurring in at least 5% of naïve patients

SPRING-2 Week 96			SINGLE Week 96		FLAMINGO Week 48		TOTAL
n (%)	TIVICAY 1/day n = 411	ISENTRESS 2/day n = 411	TIVICAY + KIVEXA 1/day n = 414	ATRIPLA 1/day n = 419	TIVICAY 1/day n = 242	PREZISTA/r 1/day n = 242	TIVICAY 1/day n = 1067
All events	**349 (85)**	**349 (85)**	**376 (91)**	**394 (94)**	**206 (85)**	**205 (85)**	**931 (87)**
Diarrhoea	57 (14)	55 (13)	84 (20)	83 (20)	**41 (17)**	**70 (29)**	182 (17)
Nausea	60 (15)	56 (14)	65 (16)	61 (15)	39 (16)	43 (18)	164 (15)
Headache	56 (14)	55 (13)	63 (15)	63 (15)	**37 (15)**	**24 (10)**	156 (15)
Nasopharyngitis	55 (13)	58 (14)	74 (18)	66 (16)	22 (9)	19 (8)	151 (14)
Insomnia	25 (6)	19 (5)	69 (17)	46 (11)	18 (7)	15 (6)	112 (10)
Fatigue	22 (5)	24 (6)	63 (15)	53 (13)	15 (6)	12 (5)	100 (9)
Upper respiratory tract infection	34 (8)	30 (7)	50 (12)	53 (13)	**13 (5)**	**23 (10)**	97 (9)
Vertigo	24 (6)	25 (6)	**40 (10)**	**153 (37)**	14 (6)	11 (5)	78 (7)
Cough	23 (6)	22 (5)	36 (9)	36 (9)	13 (5)	17 (7)	72 (7)
Depression	26 (6)	19 (5)	31 (7)	34 (8)	11 (5)	6 (2)	68 (6)
Fever	23 (6)	25 (6)	26 (6)	27 (6)	13 (5)	14 (6)	62 (6)
Back pain	21 (5)	26 (6)	30 (7)	18 (4)	9 (4)	12 (5)	60 (6)
Bronchitis	24 (6)	22 (5)	28 (7)	26 (6)	5 (2)	13 (5)	57 (5)
Vomiting	16 (4)	19 (5)	26 (6)	24 (6)	14 (6)	15 (6)	56 (5)
Sinusitis	25 (6)	17 (4)	22 (5)	15 (4)	6 (2)	12 (5)	53 (5)
Rash	19 (5)	22 (5)	**19 (5)**	**60 (14)**	9 (4)	15 (6)	47 (4)
Anxiety	17 (4)	22 (5)	26 (6)	30 (7)			43 (4)
Syphilis	22 (5)	29 (7)	18 (4)	25 (6)			40 (4)
Anogenital warts	17 (4)	23 (6)	21 (5)	19 (5)			38 (4)
Influenza	16 (4)	24 (6)	**22 (5)**	**10 (2)**			38 (4)
Abnormal dreams			**31 (7)**	**73 (17)**			31 (3)
Pharyngitis	22 (5)	14 (3)			7 (3)	12 (5)	29 (3)
Arthralgia			23 (6)	20 (5)	5 (2)	11 (5)	28 (3)
Oropharyngeal pains	19 (5)	16 (4)	27 (7)	16 (4)			46 (4)
Pain in the extremities			**22 (5)**	**10 (2)**			22 (2)
Gastroenteritis			21 (5)	17 (4)			21 (2)
Respiratory tract infection	19 (5)	12 (3)					19 (2)
Drowsiness			**9 (2)**	**24 (6)**			9 (1)

Table 11: Incidence of AEs occurring in at least 5% of experienced patients

SAILING Week 48			VIKING-3 Week 24	VIKING-4 day 8		TOTAL
n (%)	TIVICAY 1/day n = 357	ISENTRESS 2/day n = 362	TIVICAY 2/day n = 183	TIVICAY 2/day n = 14	Placebo n = 16	TIVICAY 50 mg 1 or 2/day n = 554
All events	280 (78)	286 (79)	147 (80)	7 (50)	2 (13)	434 (78)
Diarrhoea	71 (20)	64 (18)	25 (14)			96 (17)
Headache	33 (9)	31 (9)	16 (9)	2 (14)	0	51 (9)
Nausea	29 (8)	29 (8)	17 (9)	3 (21)	0	49 (9)
Upper respiratory tract infection	38 (11)	29 (8)	9 (5)			47 (8)
Cough	33 (9)	24 (7)	13 (7)			46 (8)
Nasopharyngitis	23 (6)	22 (6)	10 (5)			33 (6)
Rash	19 (5)	18 (5)	10 (5)			29 (5)
Fatigue	15 (4)	24 (7)	12(7)			27 (5)
Urinary tract infection	26 (7)	18 (5)				26 (5)
Influenza	24 (7)	25 (7)				24 (4)
Vomiting	20 (6)	20 (6)				20 (4)
Upper abdominal pain	17 (5)	5 (1)		2 (14)	0	19 (3)

Bronchitis			13 (7)			13 (2)
Fever			13 (7)			13 (2)
Arthralgia	10 (3)	18 (5)				10 (2)
Pain at the injection site			9 (5)			9 (2)
Insomnia			9 (5)			9 (2)
Vertigo				2 (14)	0	2 (0)

8.3.2 SPC/EPAR data:

Creatinine clearance (SPC):
"Increases in serum creatinine occurred within the first week of treatment with TIVICAY 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."

Lipid metabolism (EPAR)
"SPRING-2 is the most suitable study for evaluating changes in blood lipids (versus raltegravir). Like other agents in the class of integrase inhibitors, dolutegravir has no effect on blood lipids. When one compares the treatments in the SINGLE study, a very similar increase – probably without any clinical relevance – is seen with the two different regimens (abacavir/3TC + dolutegravir and tenofovir / FTC / efavirenz)."

08.4 Other data

The company has presented the unpublished report of a network meta-analysis which sought to compare the efficacy and safety of TIVICAY with those of the other three reference agents at treatment initiation in naïve patients: boosted PIs (darunavir/r, lopinavir/r, atazanavir/r), NNRTIs (efavirenz, rilpivirine), and INIs (raltegravir, elvitegravir/cobicistat).

This meta-analysis included 28 studies with in particular three randomised studies evaluating TIVICAY in adult patients: SPRING-2 (versus ISENTRESS), SINGLE (versus ATRIPLA), and FLAMINGO (versus PREZISTA/r). According to the authors, "this network meta-analysis suggests that dolutegravir could have a favourable profile compared with the three other reference agents (ATV/r, LPV/r, RPV, and EVG/c) even if the direct comparison studies remain the reference for evaluating the various treatment options. In summary, this analysis shows dolutegravir to be a first-line option for antiretroviral treatment-naïve patients."

08.5 Usage/prescription data

The proprietary medicinal product TIVICAY was subject to ATU nominatives from 14 December 2011 to 24 November 2013 (ATU decree of 27/01/2014): 91 initial ATUs were granted from the start of the ATU, 83 patients were treated with dolutegravir 50 mg, and 175 renewals were approved.

The HIV-infected patients for whom the ATU nominatives for dolutegravir were issued were all experienced patients, with no treatment alternative – essentially patients with genotypic resistance to raltegravir or intolerance to it, while having previously had several unsuccessful lines of treatment. The demographic characteristics are in agreement with those found in the clinical trials: 78% of patients were aged from 40 to 60 years, the median age was 49 years, and the majority of patients were male (70%).

Over the period under consideration, 9 serious cases corresponding to 8 patients and 15 adverse events were notified. Of the 9 serious cases, 7 were unexpected, going by the treatment information intended for the prescriber.

Four cases of serious adverse events were related to the treatment with dolutegravir:

- emergent resistance to the treatment (certain attribution);
- immune reconstitution syndrome (certain attribution);
- acute renal failure (doubtful attribution);
- depressive syndrome (possible attribution).

Two deaths following serious adverse events were reported: aggravation of progressive multifocal leukoencephalopathy associated with immune reconstitution syndrome and coma in a 41-year-old man and septic shock following MI and cardiorespiratory arrest in a 56-year-old man.

08.6 Summary and discussion

- **Efficacy**

1. **<u>Antiretroviral treatment-naïve adult patients infected with HIV-1</u>**

TIVICAY (dolutegravir) was evaluated in antiretroviral treatment-naïve adults infected with HIV-1 in three Phase III, double-blind, randomised, studies versus active comparators (SPRING-2 study: TIVICAY versus ISENTRESS, and SINGLE study: TIVICAY versus ATRIPLA) or in open-label mode (FLAMINGO study: TIVICAY versus PREZISTA/r).

In the SPRING-2 study, the patients received, in double-blind mode, TIVICAY (n = 411) once daily or ISENTRESS (n = 411) twice daily in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (TRUVADA or KIVEXA). In the SINGLE study, patients received, in double-blind mode, TIVICAY in combination with KIVEXA once daily (n = 414) or ATRIPLA (n = 419) once daily. In both studies, the clinical and demographic characteristics of patients were comparable at baseline in both treatment groups: median age from 35 to 37 years, the majority were male (about 85%), viral load ≤ 100,000 copies/ml in 70% of patients and median baseline CD4+ cells count of about 360 cells/mm^3. More than 80% of patients were in stage A (asymptomatic) of the infection.

In the FLAMINGO study patients received, in open-label mode, TIVICAY (n = 242) once daily and PREZISTA/r (n = 242) once daily in combination with TRUVADA or KIVEXA. The demographic and clinical characteristics were similar in both groups: median age of 34 years, the majority were male (85%), median viral load of 4.48 log_{10} copies/ml (viral load ≤ 100,000 copies/ml for 75% of patients) and the median CD4+ cells count was 400 /mm^3.

As regards virological response at week 48 in the PP population and in the ITT-E population, the non-inferiority of TIVICAY compared with ISENTRESS and PREZISTA/r was demonstrated:
- TIVICAY versus ISENTRESS: 90% versus 88%, difference of +1.6%; 95% CI [-2.7; 5.9] (ITT-E: 88% versus 85%; +2.4% [-2.2; 7.1]);
- TIVICAY versus PREZISTA/r: 91% versus 84%, difference of +7.4 [1.4; 13.3] (ITT-E: 90% versus 83%; +7.1% [0.9; 13.2]).

The superiority of TIVICAY over ISENTRESS (per protocol analysis) was not demonstrated in the SPRING-2 study.
The superiority of TIVICAY over PREZISTA/r (per protocol analysis) was demonstrated in the FLAMINGO study (lower limit of the 95% CI > 0). However, this superiority needs to be interpreted with caution, given the open-label nature of the study.

The non-inferiority of TIVICAY + KIVEXA in relation to ATRIPLA was demonstrated in the SINGLE study in the PP population and in the ITT-E population: 90% versus 81%; difference of +8.7%; 95% CI [+3.9; +13.4] (ITT-E: 88% versus 81%; +7.4% [2.5; 12.3]). The superiority of TIVICAY over ATRIPLA (per protocol analysis) was demonstrated.

However, it should be pointed out that ATRIPLA does not have Marketing Authorisation in Europe in the treatment of HIV-1 infection in naïve subjects. Its European Marketing Authorisation is restricted to "virologically-controlled adult subjects (with a viral load < 50 copies/ml) for more than three months with an antiretroviral combination". Also, this study cannot be considered to lend itself to practical application.

In total, in antiretroviral treatment-naïve patients and in combination with two NRTIs, TIVICAY (dolutegravir) is non-inferior to ISENTRESS (raltegravir) and to PREZISTA/r (darunavir/ritonavir) in terms of virological response at week 48 of treatment.

2. Experienced adult patients infected with HIV

In experienced patients, TIVICAY was evaluated in three Phase III studies, two of which were double-blind, randomised controlled studies (SAILING versus raltegravir and VIKING-4 versus placebo) and one uncontrolled (VIKING-3).

Experienced, integrase inhibitor-naïve adults in virological failure

The SAILING study compared the efficacy of dolutegravir (TIVICAY) once daily versus raltegravir (ISENTRESS) twice daily in experienced patients who had never received any integrase inhibitor. A total of 715 patients (mITT-E) were included in the SAILING study (354 in the TIVICAY group versus 361 in the ISENTRESS group).
At baseline, the clinical and demographic characteristics of patients were comparable in both groups: median age of 42 and 43 years, the majority were male (about 70%), comparable median viral load (with almost 70% of patients having a viral load ≤ 50,000 copies/ml) and median baseline CD4+ cells count of about 200 /mm^3. Almost half the patients were at the AIDS stage of the infection, resistant to at least three classes of ARVs (46% in the DTG group and 50% in the RAL group). The optimised treatments (OTs) received during the study were similar in both groups.

The non-inferiority, in terms of virological response at 48 weeks (viral load < 50 copies/ml), of TIVICAY in relation to ISENTRESS was demonstrated in the PP population with a 73% response in the DTG group versus 66% in the RAL group; difference +7.5%, 95% CI [0.6; 14.3]), and in the mITT-E population (71% versus 64%; difference +7.4% [0.7; 14.2]). The superiority of TIVICAY over ISENTRESS (analysis as per the protocol) in experienced integrase inhibitor-naïve patients was demonstrated in this study (lower limit of 95% CI of the difference > 0).

The immunological response was comparable in both groups, with an increase in the CD4+ cells count of 144 /mm^3 in the DTG group versus 137 /mm^3 in the RAL group.

Experienced adults in virological failure, presenting resistance to INIs and to at least two other classes of ARVs

A total of 183 patients were included in the non-comparative VIKING-3 study and 30 patients in the randomised VIKING-4 study (14 in the DTG group and 16 in the placebo group). Patient characteristics were comparable in the treatment groups in the VIKING-4 and VIKING-3 studies: median age of 48-49 years, majority of males (80%). The proportion of patients with a viral load > 50,000 copies/ml was smaller in the VIKING-4 study (14% dolutegravir group, 28% placebo group) than in the VIKING-3 study (61%).

TIVICAY, in combination with the patient's baseline treatment, reduced the mean viral load between the baseline value and the Day 8:
- VIKING-3: -1,43 $\log_{10}$ copies/ml 95% CI [-1.52; -1.34], $p < 0.001$.
- VIKING-4: -1.06 $\log_{10}$ copies/ml in the TIVICAY group compared with +0.10 $\log_{10}$ copies/ml in the placebo group and regardless of the mutation profile compared with the placebo group (ITT-E, difference -1.16; 95% CI [-1.52; - 0.80]; $p < 0.001$). Only Q148 mutations together with at least two secondary mutations seem to diminish treatment response (-0.64 $\log_{10}$ copies/ml in the dolutegravir group).

The virological response at week 24 was described only in the VIKING-3 study, with 63% (126/183) of patients having a viral load < 50 copies/ml. This response rate was variable, in cases of primary mutation to INIs and according to the category of resistance documented. The antiviral activity of dolutegravir was lower in patients with a Q148 resistance profile to INI than in patients with a non-Q148 resistance profile (including primary mutations N155H, Y143C/H/R). The analysis report at week 24 of VIKING-4 was not presented.

3. HIV-infected adolescent patients aged > 12 years

In the population covered by the Marketing Authorisation (children from 12 to 18 years), dolutegravir was evaluated in a non-comparative Phase I/II study in 23 HIV-1-infected experienced but integrase inhibitor-naïve children and adolescents aged from 12 to 18 years.

The interim analysis only covers Cohort I (23 patients from 12 to 18 years) up to 24 weeks. At 24 weeks, 16 out of 23 adolescents (70%) treated with TIVICAY once daily (35 mg: n = 4, 50 mg: n = 19) in combination with an optimised background treatment had a viral load < 50 copies/ml. Four subjects were in virological failure, none having had INI resistance at the time of virological failure. In this study, the oral dose of 50 mg of TIVICAY once daily could result in exposure comparable with that observed in adults after receiving a dose of 50 mg of dolutegravir orally once daily.

Although the clinical data for dolutegravir in experienced children and adolescents are limited, the safety profile in the paediatric population was similar to that observed in experienced adults. There are no clinical data available in treatment-naïve children and adolescents or which compare with other antiretrovirals.

- **Resistance**

In terms of resistance, the results of the *in vitro* studies and of the clinical studies with TIVICAY show that the genetic barrier to dolutegravir resistance is higher than that of raltegravir and efavirenz.
Among patients in virological failure and included in the resistance analysis:
- at week 96, no patients (0/22) developed at least one resistance mutation in the TIVICAY group, versus 5/29 (or 17%) in the ISENTRESS group (SPRING-2);
- at week 96, no patients (0/18) developed at least one resistance mutation in the TIVICAY group, versus 5/17 (or 29%) in the ATRIPLA group (SINGLE);
- at week 48, no patients (0/2 in each group) developed at least one resistance mutation in the TIVICAY and PREZISTA/r groups (FLAMINGO).

In experienced but integrase inhibitor-naïve adult patients (SAILING), INI mutations were discovered in 4 patients (or 1%) in the dolutegravir group versus 17 (or 5%) in patients in the raltegravir group.

In the presence of resistance to the class of INIs (VIKING-3) and in virological failure patients, 15 had viral strains with resistance mutations that appeared under treatment, 4 of which had a Q148 profile on failure. The emergence of resistance to dolutegravir under treatment was observed predominantly in patients with a history of Q148 mutation (at inclusion or historically).

- **Safety**

The safety data are based on the short- and medium-term results of clinical trials at week 24, 48, and 96 .
The incidence of adverse events considered to be treatment-related was:
- comparable in the dolutegravir and raltegravir groups in the SPRING-2 study (30% TIVICAY versus 29% ISENTRESS) and SAILING study (20% TIVICAY versus 23% ISENTRESS); and of the order of 25% in patients treated with TIVICAY twice daily in the VIKING-3 study.
- lower with TIVICAY + KIVEXA than with ATRIPLA in the SINGLE study (44% versus 67%).
- lower with TIVICAY than with PREZISTA/r in the FLAMINGO study (33% versus 48%).

The most common adverse events (> 10%) in patients treated with TIVICAY were: nausea, diarrhoea and headache, nasopharyngitis and insomnia. The incidence of treatment discontinuations due to treatment-related adverse events was low (2 to 3%) in all the groups treated with dolutegravir. The frequency of serious adverse events considered to be treatment-related was low (< 1%): 2 hypersensitivity reactions, 2 cases of hepatotoxicity, 1 arrhythmia, 1 attempted suicide, 1 myositis associated with acute renal failure, 1 grade 3 pruritus associated with grade 2 rash, 1 grade 3 skin eruption associated with grade 3 hyperbilirubinaemia, and grade 2 elevated ALAT.

In all the experienced populations, the safety profile of dolutegravir was comparable overall with that observed in antiretroviral treatment-naïve patients.
Overall, the safety profile of dolutegravir was similar to that of raltegravir and better than that of PREZISTA/r and ATRIPLA.

08.7 Planned studies

The Risk Management Plan provides for the monitoring and assessment of all identified and potential risks through the pharmacovigilance plan and in particular: an observational and prospective cohort study of the risk of hypersensitivity reactions, hepatotoxicity, and severe rash, a phototoxicity study, an analysis of psychiatric adverse events in the pharmacovigilance reports (PSURs), and routine pharmacovigilance activity.

The following planned studies are currently under development:

Study	Target population	Design	n	Reports
ARIA ING117172	ARV-naïve adult women with HIV-1 Evaluate the efficacy and safety of the fixed-dose combination DTG 50 mg/ABC/3TC once daily vs. ATV/r 300 mg once daily + TDF/FTC	Phase IIIb multicentre, randomised, parallel-group, open-label, controlled, non-inferiority study comparing DTG/ABC/3TC vs. ATZ/r + TDF/FTC at week 48	n = 474	In progress
ODISSEY PENTA 20	HIV-1-infected children and adolescents under 18 years Evaluate the efficacy and safety of DTG once daily +	Phase II/IIIb multicentre (African and non-African), randomised, parallel-group, open-label, controlled, non-inferiority study	n = 500	Starting during 2014

	2 NRTIs vs. 1st- and 2nd-line reference treatment	comparing DTG + 2 NRTIs with a 1st- and 2nd- line reference treatment (PI or NNRTI) lasting week 96		
Study in Pregnant Women ING200336	Women becoming pregnant under the fixed-dose combination DTG/ABC/3TC during the course of the ARIA study Evaluate the PK, safety, and toxicity	Phase IIIb trial International multicentre Non-comparative	n = 12	In progress
Post-exposure prophylaxis	Homosexual males not infected with HIV-1 or of unknown status who have taken part in 'at risk' behaviours Evaluate the safety and compliance of the combination DTG + TDF/FTC	Phase III non-comparative study Australia Evaluating DTG + TDF/FTC once daily for 28 days	n = 100	Starting during 2014

09 THERAPEUTIC USE

- **Reference therapeutic strategy**

The scientific data acquired on HIV and its treatment methods have been taken into account.[10] Numerous antiretrovirals, in six drug categories, are available: nucleoside/tide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), CCR5 receptor antagonists (anti-CCR5), and integrase inhibitors (INI) (cf. **Table 2**).

1. Antiretroviral treatment in naïve adults

At the present time, therapeutic combinations combining at least three highly active agents are recommended in naïve subjects, using one of the following regimens:
- 2 NRTIs + 1 PI;
- 2 NRTIs + 1 NNRTI.

The choice of the two NRTIs for triple therapy should preferably involve fixed combinations of tenofovir/emtricitabine (TRUVADA) or abacavir/lamivudine (KIVEXA).
TRUVADA should be preferred if the plasma viral load is ≥ 100,000 copies/ml, particularly in the case of combination with atazanavir/ritonavir (REYATAZ) or efavirenz (SUSTIVA), owing to the greater risk of virological failure with KIVEXA in this subpopulation (results of study ACTG A5202).
When the viral load is < 100,000 copies/ml, the choice between KIVEXA and TRUVADA can be made on a case-by-case basis and must take account of factors such as: HBV co-infection and renal impairment.

TRUVADA must be used with caution in patients with renal impairment or who are at risk of this occurring. KIVEXA can only be used in patients who are not carriers of allele HLA B*5701.
The third agent should preferably be a PI/ritonavir or an NNRTI. There is no conclusive argument in favour of the use of one of these two classes over the other: atazanavir/r, darunavir/ (IP/r), efavirenz, or rilpivirine (NNRTI).

Triple therapy with an INI as the 3rd agent
The tenofovir/emtricitabine + raltegravir combination is possible as a start of ARV treatment in naïve patients, but is not one of the preferred combinations referred to previously. Elvitegravir and

[10] Medical management of individuals infected with HIV. Recommendation of the group of experts. 2013 Report under the guidance of Prof. Philippe Morlat and under the auspices of the CNS [French national council on AIDS] and the ANRS [National AIDS research agency] http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf.

dolutegravir did not form part of the therapeutic strategy because they only came onto the market after the publication of the 2013 guidelines. However, elvitegravir/cobicistat (as a fixed-dose combination in STRIBILD) and dolutegravir (TIVICAY) are mentioned as possible alternatives owing to "their efficacy and good safety".[10]

2. Antiretroviral treatment in experienced adult subjects with virological failure

With the currently available ARVs, the goal of controlling viral replication (VL < 50 copies/ml) is in most cases achievable, even in persons with a long ARV history and in the presence of more than one class of resistance mutations. Whenever possible, preference should be given to combinations that have been evaluated in therapeutic trials. The optimum situation is when a treatment regimen can be put together comprising three active medicinal products, based on the treatment history and cumulative genotype.

To be considered an active ARV it must:
– belong to a class as yet not used;
– belong to a class that has been used, but whose current and cumulative resistance genotype(s) give the impression that this ARV is active.

The new treatment will preferentially combine an active PI/r (essentially darunavir/r in two daily intakes of 600 mg, more rarely tipranavir/r; the combination of two PIs is not recommended), with two other active ARVs, including dolutegravir (TIVICAY).

3. Initiating treatment in the paediatric population (preferred choices in naïve subjects)

"Preferred choice: at all ages and regardless of the initial immunovirological parameters, the preferred choice is a combination of two NRTIs and one PI/r.
Preferred PI/r: before the age of 6 years, lopinavir/r is the preferred choice on account of its suitable pharmaceutical form, the data relating to neonates, and the feedback on its use in paediatric patients. On the other hand, this compound is contraindicated in premature neonates. After the age of 6 years, lopinavir/r or atazanavir/r may be recommended.
Preferred NRTIs: the zidovudine + lamivudine, abacavir + lamivudine, or zidovudine + abacavir combinations may be recommended. However, the zidovudine + abacavir combination is preferred because of its strong genetic barrier in infants under 24 months or children at high risk of not fully complying with treatment. The risk of hypersensitivity to abacavir is sufficient to justify systematic investigation of the HLA-B*5701 group before prescribing it.
Other possible choices of PI: darunavir/r (forthcoming Marketing Authorisation in naïve children ≥ 12 years), fosamprenavir/r (age ≥ 6 years).

Alternative choice: combination of two NRTIs and one NNRTI, provided there is good treatment compliance from the outset".

4. Antiretroviral treatment in experienced children and adolescents aged from 12 to 18 years, who are in virological failure situations

A significant proportion of children are clinically asymptomatic, with no immune deficiency, but in "virological failure" with persistent viral replication. The risk of selecting a resistant virus then depends directly on the choice of compounds. As already mentioned, treatment that includes an NNRTI will inevitably lead to resistance to this class, even including – in cases of prolonged replication – resistance to new compounds (etravirine). Such resistance may also apply to NRTIs, especially lamivudine, which also has a low genetic barrier to resistance. As in adults, even low viral replication levels can lead to the emergence of resistant viruses. Conversely, any premature change in treatment can quickly lead to a situation of viral multiresistance and exhaustion of available treatment resources. Before considering any change in treatment, it is essential to be satisfied that the treatment is being adhered to, to carry out determinations of the antiretroviral levels, and to be aware of the treatment history and of previous resistance genotypes, following the example of what is recommended in adults in this situation.

The factors associated with a greater chance of virological success of the new treatment are a moderately elevated viral load (< 30,000 copies/ml), an elevated CD4 count, the use of a protease inhibitor potentiated by ritonavir, and the use of a new class of ARV not previously received by the patient.

- **Role of dolutegravir therapeutic strategy**

Antiretroviral therapy-naïve patients

In this population, it is currently recommended to use preferentially two NRTIs combined with an NNRTI (ideally efavirenz, or rilpivirine only in patients with a low viral load ≤ 100,000 copies/ml), or a PI (darunavir, atazanavir). The currently available INIs (raltegravir or elvitegravir) are not included among the first-line preferred options.

The incidence of neuropsychiatric disorders in patients treated with efavirenz and the low genetic barrier of NNRTIs (efavirenz and rilpivirine), a single mutation being sufficient to lead to resistance, could encourage preferential use of dolutegravir in place of an NNRTI.

Compared with other INIs, the ease of use of dolutegravir (a single daily intake) and its higher genetic barrier compared with raltegravir (ISENTRESS) should see its eventual replacement by dolutegravir. The necessity of a booster and the low genetic barrier of elvitegravir (STRIBILD), lower than that of raltegravir and of dolutegravir, limits the benefit of this compound.

On the other hand, dolutegravir loses its advantage of a single daily intake in the case of viruses resistant to INIs (raltegravir, elvitegravir), but susceptible to dolutegravir.

Experienced patients (with virological failure)

In these circumstances, treatment depends on the virus genotyping resistance.

In treatment-experienced patients whose virus doesn't have INI resistance mutations, dolutegravir should be preferred to raltegravir owing to its greater ease of use and higher genetic barrier. Elvitegravir has not shown any efficacy in these situations and is not recommended.

On the other hand, it would seem premature, because of a weaker effect on cholesterol, to prefer dolutegravir over a PI (in particular darunavir) in this situation simply because PIs have a high genetic barrier. According to the Morlat guideline, the new treatment will preferentially combine an active PI/r (essentially darunavir/r in two daily intakes of 600 mg, more rarely tipranavir/r; the combination of two PIs is not recommended), with two other active ARVs, including dolutegravir.

Dolutegravir has also demonstrated an efficacy in experienced patients who have no therapeutic options and whose virus is susceptible to dolutegravir, and thus represents in these patients the therapeutic option of choice.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual Benefit

◗ HIV infection is a serious, life-threatening pathology.

◗ This proprietary medicinal product is designed to prevent and/or correct the immune deficiency brought on by HIV infection.

◗ The efficacy/adverse effects ratio is high when used in association with other antiretrovirals.

◗ Alternative medicinal products exist.

◗ It is a first-line therapy.

◗ Public health benefit:
The public health burden of HIV-1 infection is substantial. In the population corresponding to the indication (adult and adolescent patients infected with HIV-1, either antiretroviral treatment-naïve or experienced, in virological failure), the burden is moderate owing to the more limited number of patients concerned in comparison with the total population of HIV patients in France.

Reducing AIDS-related morbidity and mortality is a public health need which is an established priority (National programme against HIV-AIDS*)

There is no information that allows the impact of TIVICAY on morbidity and mortality or on quality of life to be estimated directly. However, in light of the available data [non-inferiority in terms of immunovirological efficacy compared with reference antiretrovirals with a favourable safety profile] and taking into account the potentially positive impact in terms of reducing the incidence of cases of resistance, the proprietary medicinal product TIVICAY is expected to have an impact on the reduction in morbidity and mortality associated with HIV-1 infection. At best, this impact would be small at the population level.

As a result, TIVICAY should be able to provide a response to the public health need identified.
It is therefore expected that the propriety medicinal product TIVICAY will benefit public health, though the benefit is slight.

*National programme against HIV-AIDS and STDs. Ministry of Health 2010-2014

In consequence, the Transparency Committee considers that the actual benefit of TIVICAY in the indication "treatment of type-1Human Immunodeficiency Virus (HIV-1) infected adults and adolescents above 12 years of age" is substantial in antiretroviral-naïve patients and in experienced patients with prior treatment failure.

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "treatment of antiretroviral treatment-naïve and experienced type-1 Human Immunodeficiency Virus (HIV-1) infected adults and adolescents above 12 years of age following failure of prior antiretroviral therapy" and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 100%**

010.2 Improvement in actual benefit (IAB)

In antiretroviral-naïve or experienced patients whose virus has no integrase inhibitor (INI) resistance mutations:
The Transparency Committee considers that TIVICAY (dolutegravir) in combination with other antiretrovirals provides a minor improvement in actual benefit (level IV) compared with raltegravir (ISENTRESS) due to having an immunological and virological efficacy that is not inferior to that of raltegravir, with a higher genetic barrier to the development of resistance and greater ease of use than raltegravir (a single dose versus two daily doses in the case of raltegravir).

In patients who have exhausted their therapeutic options and whose virus is susceptible to dolutegravir:
The Transparency Committee considers that TIVICAY (dolutegravir), in combination with an optimised background treatment, provides a moderate improvement in actual benefit (level III) in terms of immunological and virological efficacy in therapeutic management.

010.3 Target population

The target population comprises treatment-naïve adult patients with HIV-1, experienced patients but in virological failure, and experienced children aged from 12 to 18 years.

The target population was estimated on the basis of the number of naïve HIV-infected persons able to start antiretroviral treatment, and on the number of experienced patients in virological failure. According to the 2013 guideline on the medical management of persons with HIV infection, effective antiretroviral (ARV) treatment should be offered to everyone living with HIV, including soon after contamination and/or when the CD4 count remains > 500/mm^3, as this brings with it benefits in terms of a reduction in morbidity and mortality and in the risk of transmission of the HIV.

Likewise, the estimate of the target population was arrived at on the basis of the number of patients already in the healthcare system.

According to these estimates, in 2010 there were 149,900 (95% CI: 134,700-164,900)[10] persons with HIV living in France. Of these, 81% were diagnosed, 74% were in the healthcare system (i.e. between 99,000 and 122,000 people). As of 31 December 2012,[11] 104,236 patients had official "ALD" (chronic condition) status for their HIV infection managed in the general scheme. Extrapolating the data from the general scheme to the whole of the population in France, the number of persons classed as having the chronic condition HIV infection can be estimated at 118,450 persons in 2012.

According to the FHDH database,[12]
- about 88% of the 118,450 persons in the French healthcare system are receiving antiretroviral combinations, i.e. 104,236 people;
- patients starting first-line treatment represent 5.4%, i.e. about 6400 naïve patients starting first-line treatment.
- of the 6.5% of patients not receiving any treatment, 4.2% had already received some but had stopped taking it, and 1.3% were receiving treatment other than a powerful antiretroviral combination, e.g. dual therapy with two NRTIs. By applying the percentage of naïve patients (6.5%) to the 118,450 under treatment for HIV infection at the end of 2012, it is estimated that there are about 7700 patients not receiving any treatment who could start taking a first-line treatment, according to the new guidelines for the management of HIV disease.

[11] CNAMTS [National Salaried Workers' Health Insurance Fund] 2013 data.
[12] FHDH - ANRS [National Agency for AIDS Research] CO4. Retour d'Informations Clinico-Épidémiologiques. June 2011. http://www.ccde.fr.

- Of the 104,236 people receiving antiretroviral combinations, 16% of the patients are in virological failure (Morlat 2013[10]), i.e. 16,678 people.

Thus, the target population could be estimated in 2014 to be 14,100 naïve patients and 16,700 experienced patients in virological failure; i.e. a total of 30,800 patients. This population could increase in the coming years, depending on the screening efforts, as this estimate does not take into account the still high proportion (20%) of HIV-infected people in France who are unaware that they are HIV positive.

In practice, the number of patients likely to receive TIVICAY as part of a triple therapy in naïve or experienced subjects will be fewer than 30,800 patients, given the existence of other currently recommended alternatives.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

It is appropriate for the prescribing conditions according to the indication, the dose, and the treatment duration.

APPENDIX

Table 1: Demographic and clinical characteristics of patients on inclusion in SPRING-2 and SINGLE (ITT-E population)

012	SPRING-2		SINGLE	
	TIVICAY DTG (n = 411)	**ISENTRESS RAL (n = 411)**	**TIVICAY + KIVEXA DTG + 3TC/ABC (n = 414)**	**ATRIPLA EFV/FTC/TDF (n = 419)**
Demographic characteristics				
Median age, *(min.-max.)*	*37 (18-68)*	*35 (18-75)*	*36 (18-68)*	*35 (18-85)*
Male *(%)*	*348 (85)*	*355 (86)*	*347 (84)*	*356 (85)*
Viral load (copies of HIV-1 RNA/ml)				
Median (log_{10})	*4.52*	*4.58*	*4.67*	*4.70*
≤ 100,000 copies/ml, n (%)	*297 (72)*	*295 (72)*	*280 (68)*	*288 (69)*
> 100,000 copies/ml, n (%)	*114 (28)*	*116 (28)*	*134 (32)*	*131 (31)*
Ly T CD4+ count (absolute value in cells/mm^3)				
Median	*359.0*	*362.0*	*334.5*	*339.0*
< 350	*199 (48)*	*189 (46)*	*220 (53)*	*221 (52)*
350 to < 500	*126 (31)*	*136 (33)*	*131 (32)*	*128 (31)*
≥ 500	*86 (21)*	*86 (21)*	*63 (15)*	*70 (17)*
CDC clinical category n (%)				
Asymptomatic (A)	*359 (87)*	*347 (84)*	*342 (83)*	*350 (84)*
Non-AIDS symptomatic category (B)	*43 (10)*	*55 (13)*	*54 (13)*	*52 (12)*
AIDS category (C)	*9 (2)*	*9 (2)*	*18 (4)*	*17 (4)*
Hepatitis B or C virus co-infection				
Hepatitis B	*7 (2)*	*8(2)*	*1 (<1)*	*1 (<1)*
Hepatitis C	*41 (10)*	*35 (9)*	*27 (7)*	*29 (7)*

Table 11: Demographic and clinical characteristics of patients on inclusion in SAILING (mITT-E population)

mITT-E	SAILING	
	TIVICAY DTG (n = 354)	***ISENTRESS RAL (n = 361)***
Demographic characteristics *n (%)*		
Median age, *(min.-max.)*	*42 (21-69)*	*43 (18-73)*
Male (%)	*247 (70)*	*238 (66)*
Viral load *(copies of HIV-1 RNA/ml)*		
Median (log_{10})	*4.17*	*4.21*
≤ 50,000 copies/ml, n (%)	*249 (70)*	*254 (71)*
> 50,000 copies/ml, n (%)	*105 (30)*	*107 (29)*
Ly T CD4+ count *(absolute value in cells/mm^3)*		
Median	*204.5*	*193.0*
< 350	*255 (72)*	*263 (73)*
350 to < 500	*56 (16)*	*59 (16)*
≥ 500	*43 (12)*	*39 (11)*
CDC clinical category *n (%)*		
Asymptomatic (A)	*111 (31)*	*114 (32)*
Non-AIDS symptomatic category (B)	*70 (20)*	*89 (25)*
AIDS category (C)	*173 (49)*	*158 (44)*
Hepatitis B or C virus co-infection *n (%)*		
Hepatitis B	*17 (5)*	*16 (4)*
Hepatitis C	*31 (9)*	*48 (13)*
Initial genotypic and phenotypic resistance *n (%)*		
Resistance to 2 classes *including NRTI+NNRTI*	*186 (53)* *132 (37)*	*178 (49)* *126 (35)*
Resistance to 3 classes *including NRTI+NNRTI+CCR5* *NRTI+NNRTI+PI*	*124 (35)* *69 (19)* *39 (11)*	*150 (42)* *66 (18)* *50 (14)*
Resistance to 4 classes *including NRTI+NNRTI+PI+CCR5*	*40 (11)* *34 (10)*	*30 (8)* *26 (7)*
Resistance to 5 classes	*4 (1)*	*3 (<1)*