Tivicay (dolutegravir) 50 mg tablets

gsk ViiV Healthcare

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

SPRING-2

Efficacy and safety of dolutegravir (DTG) in treatment-naïve subjects

IL/DLG/0039/14 June 2014
GSK (Israel) Ltd. Basel 25, Petach Tikva. Tel-03-9297100
Medical information service: il.medinfo@gsk.com
Adverse events reporting service: il.safety@gsk.com, Tel: 03-9297100

PHASE III DTG TRIALS IN TREATMENT-NAÏVE ADULT SUBJECTS WITH HIV

SINGLE[1] — N=833

Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of:
- DTG (50 mg QD) with ABC/3TC FDC plus ATRIPLA® placebo
- ATRIPLA®(QD) plus DTG and ABC/3TC FDC placebo

FLAMINGO[2] — N=484

Phase IIIb non-inferiority, randomised, active-controlled, multicentre, open-label study of:
- DTG (50 mg QD) + 2 NRTIs
- DRV/r (800 mg*/100 mg QD) + 2 NRTIs

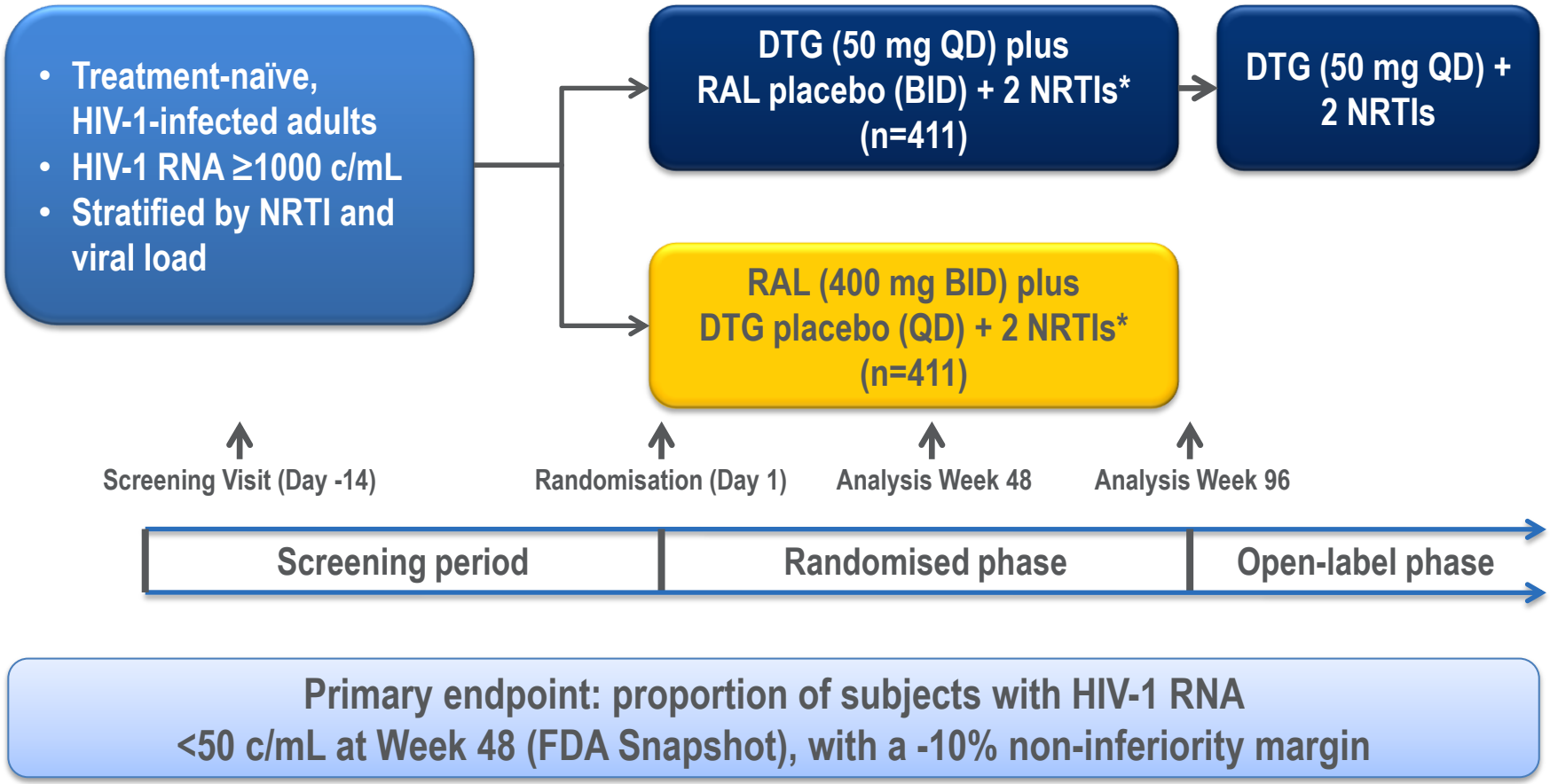
SPRING-2[3,4] — N=822

Phase III non-inferiority, randomised, double-blind, double-dummy, multicentre study of:
- DTG (50 mg QD) plus RAL placebo (BID) + 2 NRTIs
- RAL (400 mg BID) plus DTG placebo (QD) + 2 NRTIs

*Given as 2 x 400 mg tablets
NRTI, nucleoside reverse transcriptase inhibitor
DRV/r, darunavir/ritonavir; QD, once daily; BID, twice daily;
FDC, fixed-dose combination

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

SPRING-2 STUDY DESIGN



Primary endpoint: proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot), with a -10% non-inferiority margin

*Investigator's selection ABC/3TC or TDF/FTC
FDA, Food and Drug Administration

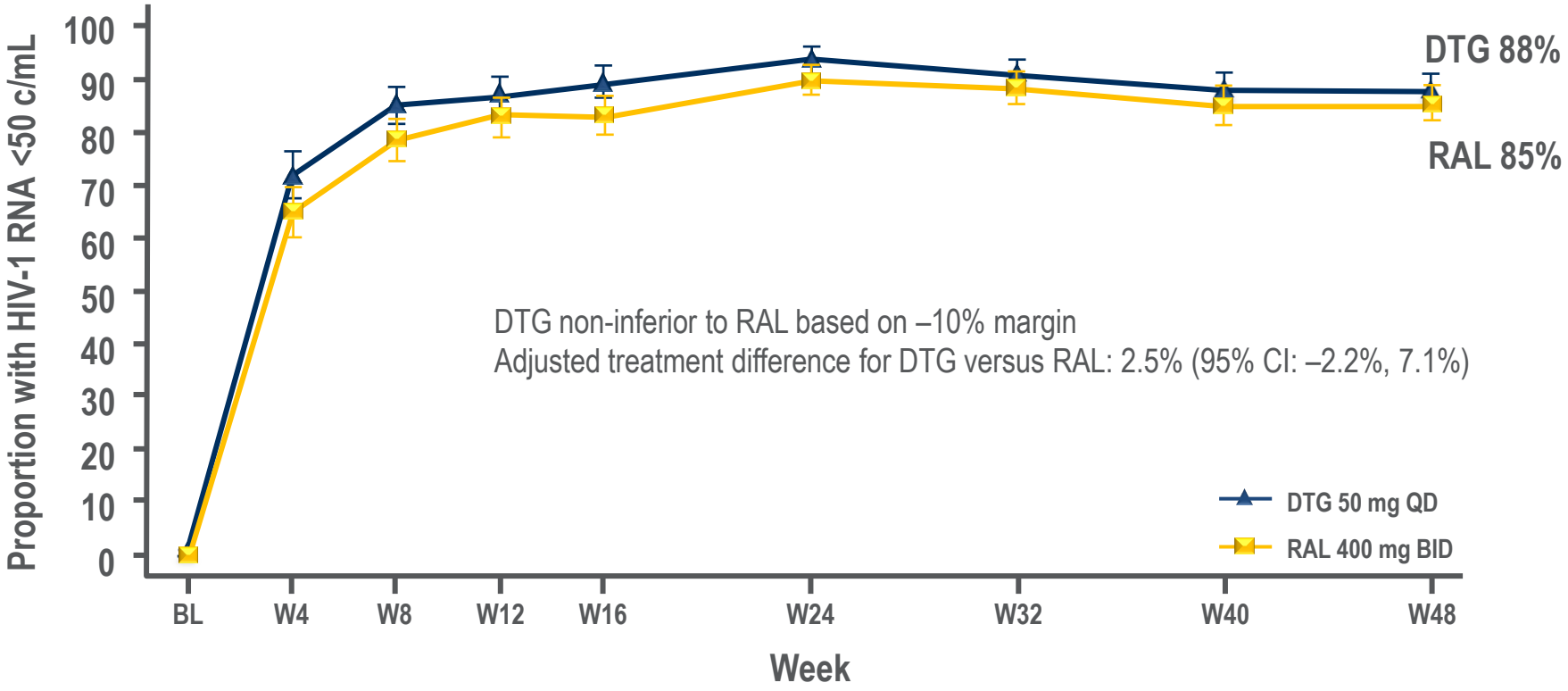
Raffi F et al. *Lancet* 2013;381:735–43

BASELINE CHARACTERISTICS

Characteristic	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)
Median age, years (range)	37 (18–68)	35 (18–75)
Male gender, n (%)	348 (85)	355 (86)
Race, %		
White	346 (84)	352 (86)
African American/African heritage	49 (12)	39 (9)
Other	16 (4)	20 (5)
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.5	4.6
>100,000 c/mL, n (%)	114 (28)	116 (28)
Baseline $CD4^+$		
Median (cells/mm^3)	359	362
<200 cells/mm^3, n (%)	55 (13)	50 (12)
Hepatitis co-infection, n (%)		
Hepatitis B	7 (2)	8 (2)
Hepatitis C	41 (10)	35 (9)
Investigator-selected dual NRTIs, n (%)		
TDF/FTC	242 (59)	247 (60)
ABC/3TC	169 (41)	164 (40)

Adapted from Table 1 in Raffi F et al. *Lancet* 2013;381:735–43

IN TREATMENT-NAÏVE PATIENTS, DTG WAS NON-INFERIOR TO RAL AT 48 WEEKS

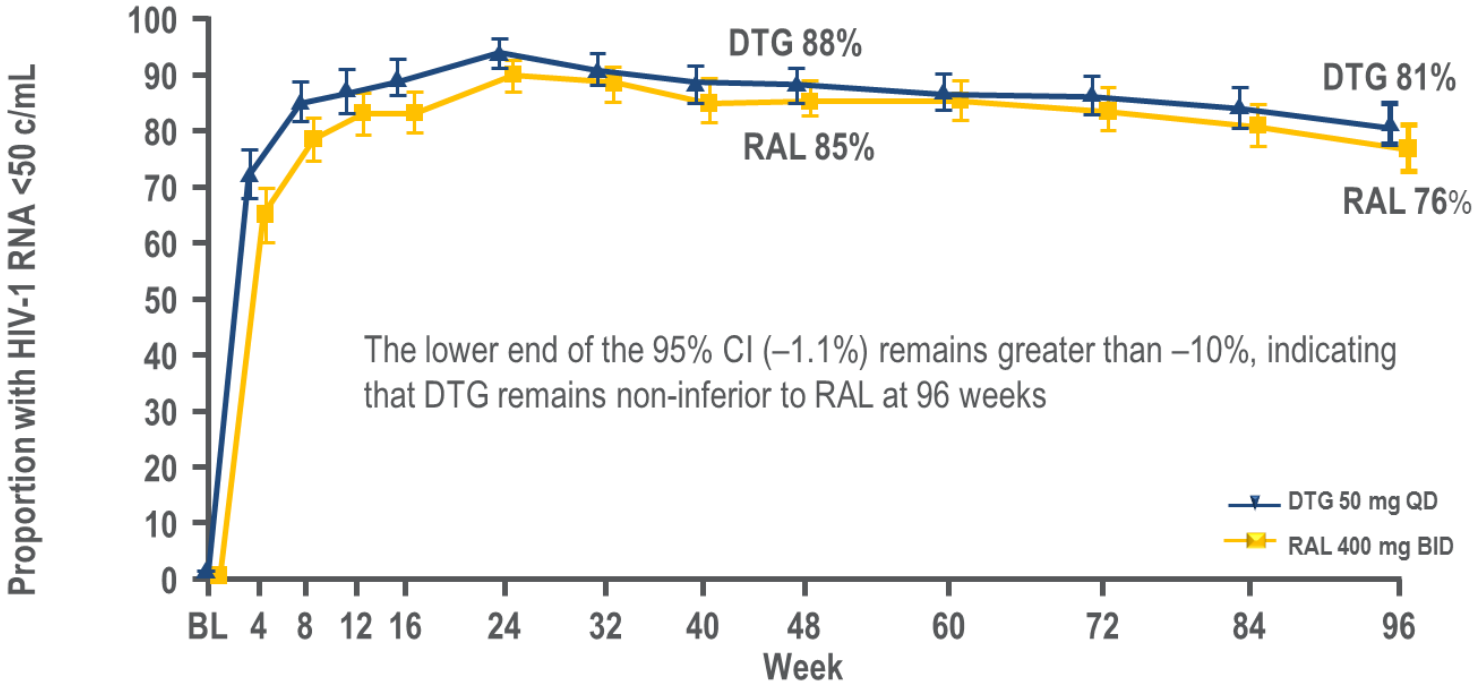


Median (IQR) Change From Baseline CD4+ Cell Count (cells/mm^3)

	Week 4		Week 24		Week 48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

1. Raffi F et al. IAS 2012. Abstract THLBB04
2. Adapted from Raffi F et al. Lancet 2013;381:735–43

IN TREATMENT-NAÏVE PATIENTS, DTG WAS NON-INFERIOR TO RAL AT 96 WEEKS



Treatment	Number of responders/ total assessed, n (%)	Difference in proportion (95% CI) (DTG - RAL)	Adjusted difference in proportion (95% CI) (DTG - RAL)
DTG 50 mg QD	332/411 (81)	4.4% (–1.2%, 10.0%)	4.5% (–1.1%, 10.0%)
RAL 400 mg BID	314/411 (76)		

DTG and RAL were associated with similar increases in CD4+ cell count from baseline over time.[1–3]

Error bars indicate 95% CI

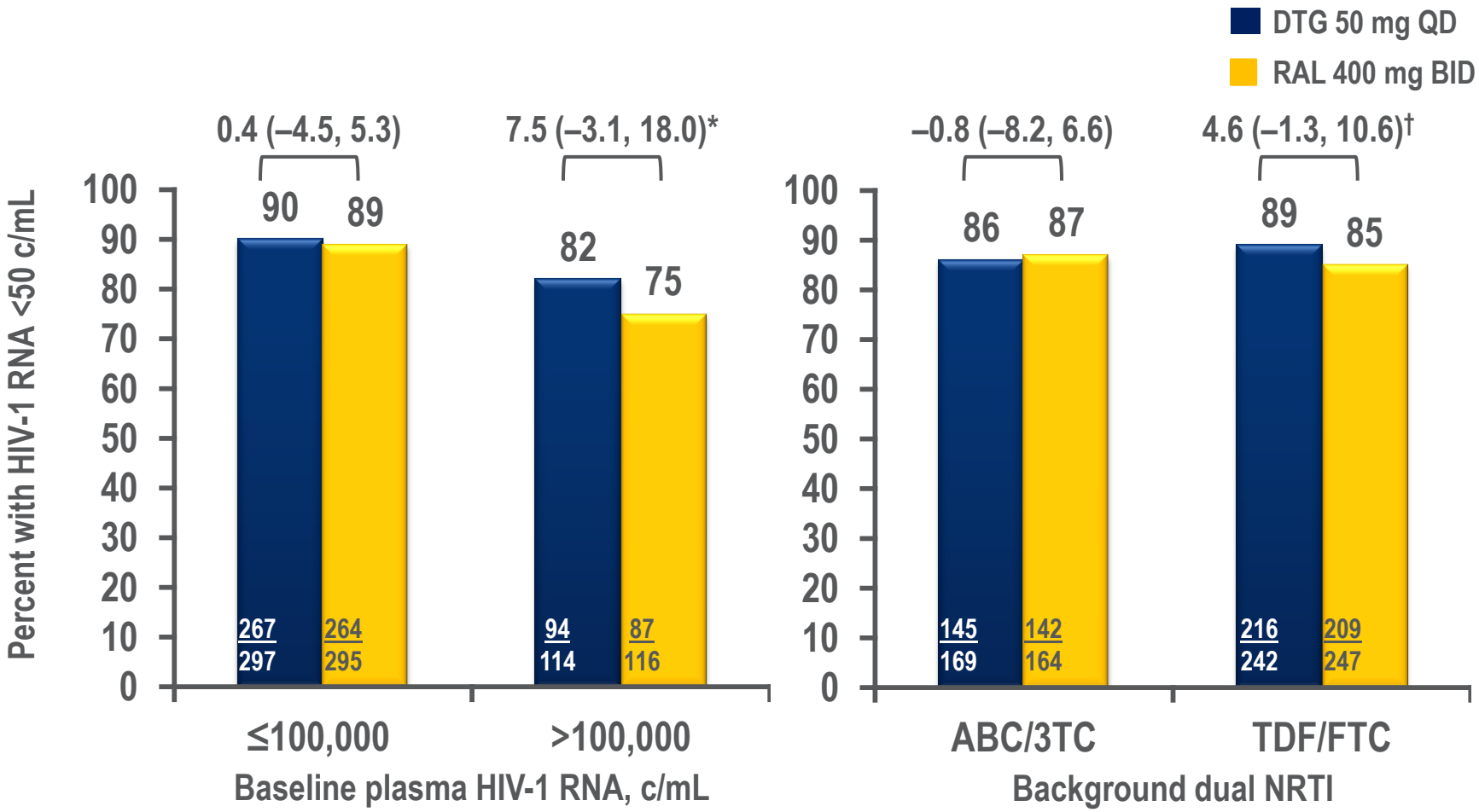
1. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
2. Raffi F et al. IAS 2013. Poster TULBPE17
3. Raffi F et al. Lancet 2013;381:735–43

VIROLOGIC RESPONSE OUTCOMES WITH DTG WERE NON-INFERIOR TO RAL AT WEEK 48

Outcome (Snapshot) at Week 48, n (%)	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)
Virologic success	**361 (88)**	**351 (85)**
Virologic non response	**20 (5)**	**31 (8)**
Data in window not <50 c/mL	8 (2)	5 (1)
Discontinued for lack of efficacy	5 (1)	13 (3)
Discontinued for other reason while not <50 c/mL	2 (<1)	11 (3)
Change in antiretroviral	5 (1)	2 (<1)
No virologic data at Week 48	**30 (7)**	**29 (7)**
Discontinued because of AE or death	9 (2)	6 (1)
Discontinued for other reasons	21 (5)	23 (6)

Adapted from Raffi F et al. *Lancet* 2013;381:735–43

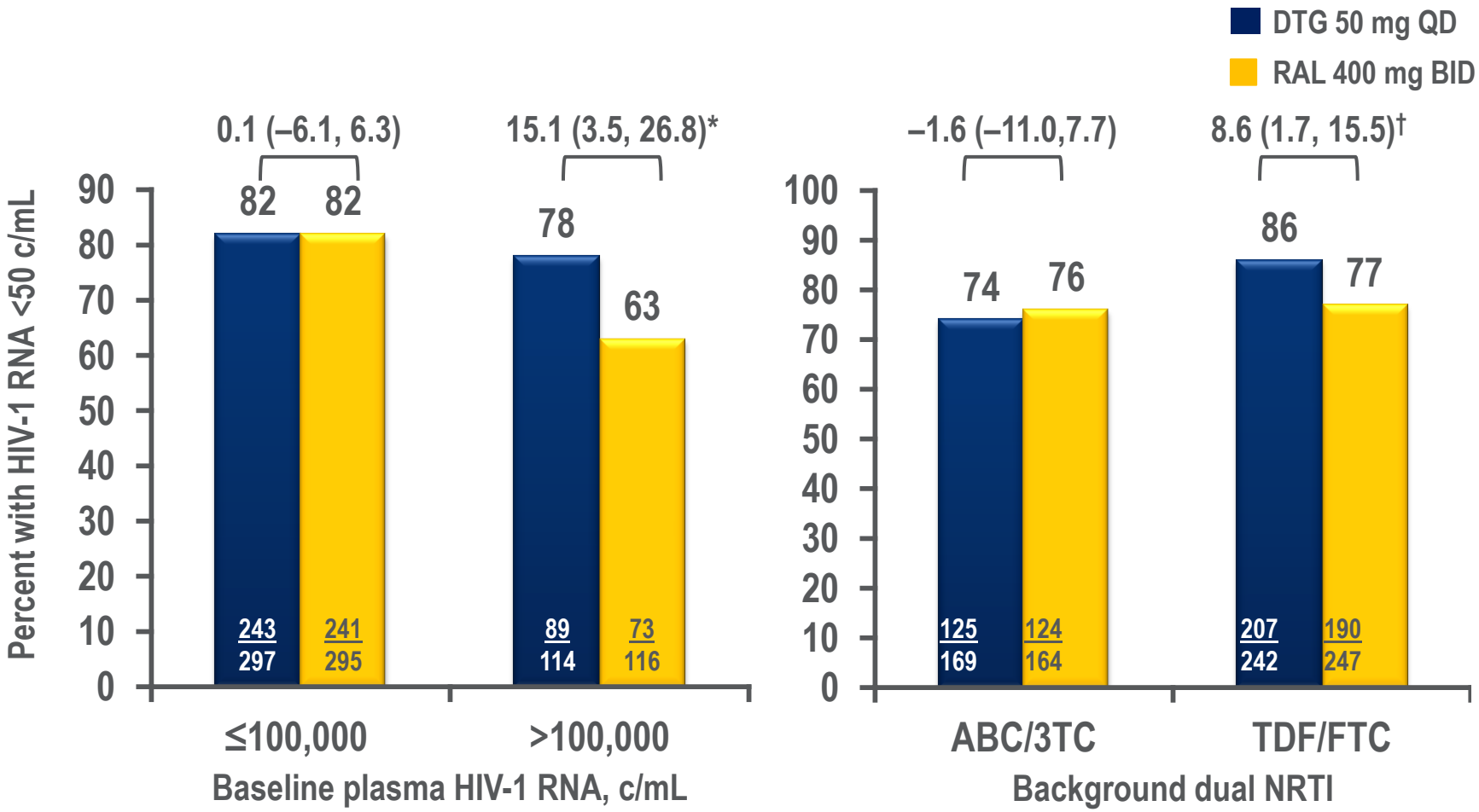
DTG EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 48)



*P=0.236; †P=0.264; p-values evaluated using a test for homogeneity

Adapted from Raffi F et al. *Lancet* 2013;381:735–43

DTG EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD OR BACKGROUND REGIMEN (WEEK 96)



*P=0.026; †P=0.083; p-values evaluated using a test for homogeneity

Adapted Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

NO INI OR NRTI RESISTANCE THROUGH 96 WEEKS WITH DTG

Amongst DTG-treated subjects, no INI- nor NRTI-resistant mutations were detected through Week 96

n (%)	DTG 50 mg QD (n=411)		RAL 400 mg BID (n=411)	
	During first 48 weeks	Between weeks 48 and 96	During first 48 weeks	Between weeks 48 and 96
Subjects with PDVF	20 (5)	2(<1)	28 (7)	1(<1)
Emergent INI-resistant mutations	0	0	1 (6)	0
NRTI-resistant mutations	0	0	4 (21)*	0

INI=integrase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PR=protease. PDVF=protocol-defined virological failure (confirmed HIV-1 RNA ≥50 c/mL on or after Week 24). RT=reverse transcriptase.

*One participant had INI-resistance mutations T97T/A, E138E/D, V151V/I, and N155H, and NRTI-resistance mutations A62A/V, K65K/R, K70K/E, and M184V; one participant had NRTI-resistance mutation M184M/I; one participant had NRTI-resistance mutation A62A/V; and one participant had NRTI-resistance mutation M184M/V

Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

AT WEEK 48 DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS

Discontinuations due to AEs were 2% for DTG vs 2% for RAL at week 48[1]

AEs, n (%)	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)
AEs leading to withdrawal[1]	10 (2)	7 (2)
Serious drug related AEs[1,3]	3 (<1) Arrhythmia, hypersensitivity, hepatitis	5 (1)* Convulsion (2), aphasia, hypersensitivity, CPK increased[3], diarrhoea
Fatal AEs[2]	1 (<1)**	1 (<1)†

Drug-related Grade 2 to 4 AEs (any event) were 6% (24/411) for DTG and 7% (27/411) for RAL[1]

* One subject experienced 2 SAEs related to study drug (increased CPK and convulsions)
** Homicide considered not related to DTG
† Suicide considered not related to RAL
AST, aspartate amino transferase

1. Adapted from Raffi F et al. IAS 2012. Abstract THLBB04
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F et al. Appendix from *Lancet* 2013;381:735–43

DTG OFFERED SIMILAR TOLERABILITY TO RAL

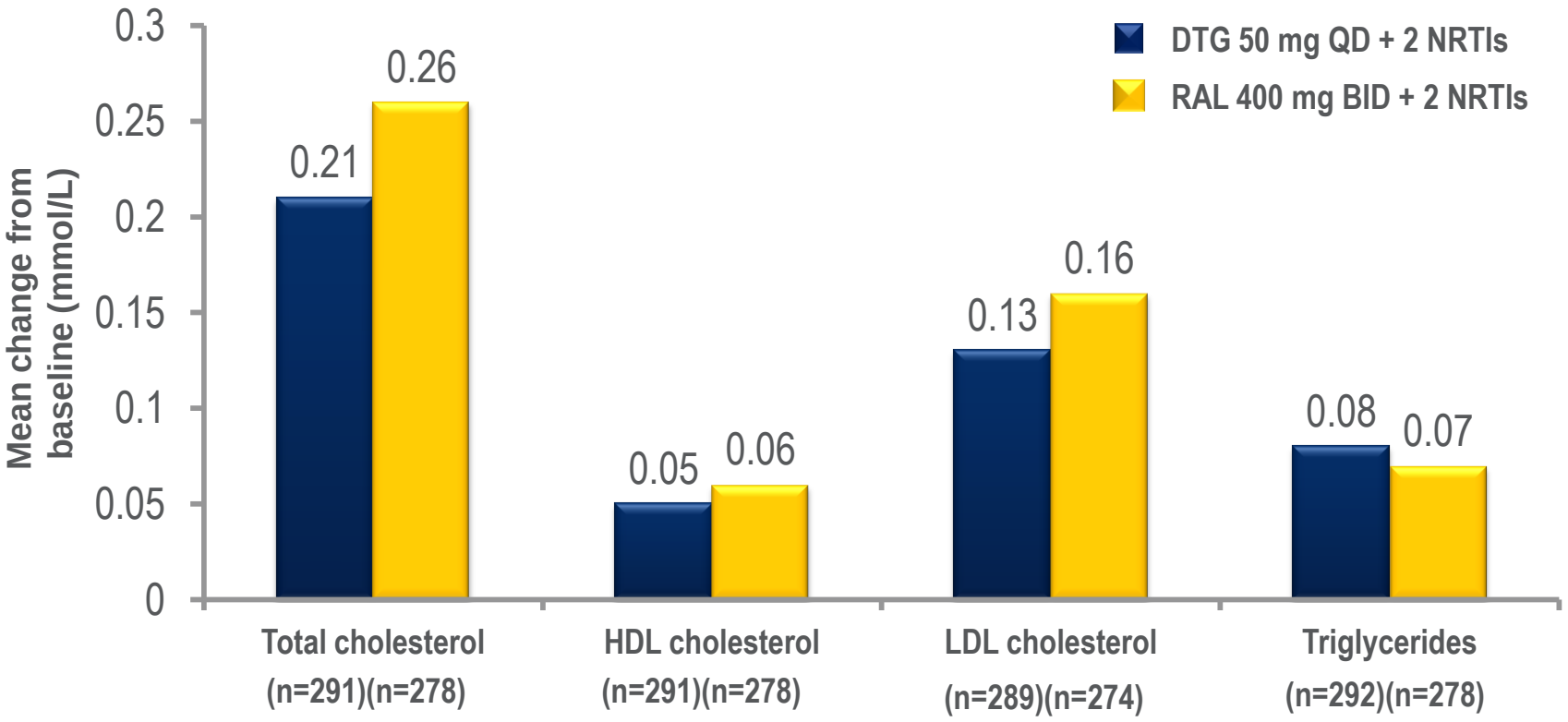
Discontinuations due to AEs were 2% for DTG vs 2% for RAL at Week 96[3]

AEs, n (%)	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)
WEEK 48[1,2]		
Any event	**339 (82)**	**340 (83)**
Nausea	59 (14)	53 (13)
Headache	51 (12)	48 (12)
Nasopharyngitis	46 (11)	48 (12)
Diarrhoea	47 (11)	47 (11)
WEEK 96[3,4]		
Any event	**349 (85)**	**349 (85)**
Nausea	60 (15)	56 (14)
Nasopharyngitis	55 (13)	58 (14)
Diarrhoea	57 (14)	55 (13)
Headache	56 (14)	55 (13)

1. Adapted from Raffi F et al. IAS 2012. Abstract THLBB04
2. Adapted from Raffi F et al. *Lancet* 2013;381:735–43
3. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35 (suppl appendix)

DTG HAD A LIPID-NEUTRAL PROFILE

No evidence of clinically significant impact on lipid profile (i.e. total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides) at 96 weeks[1]

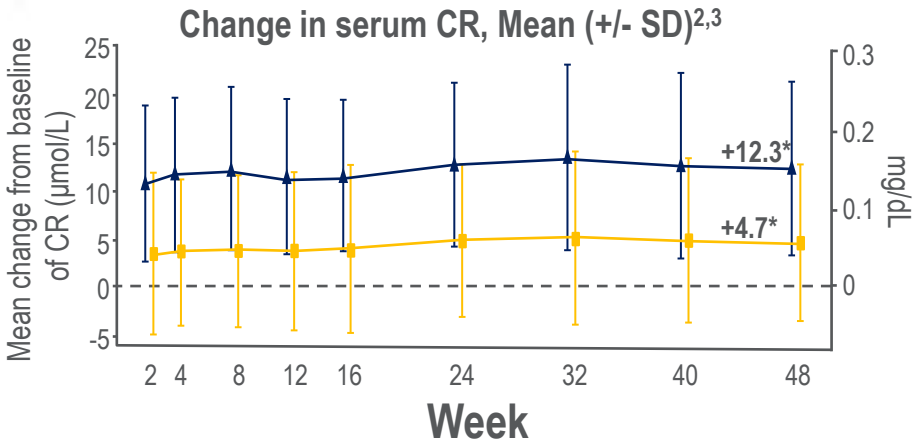


Median changes at Week 48 in mmol/L: Total cholesterol, DTG, +0.18 mmol/L, RAL +0.23 mmol/L; Triglycerides, DTG +0.10 mmol/L, RAL +0.10mmol/L
IQR, interquartile range

1. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
2. Data on file. UK/DLG/0028/13,01/11/13

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged[1]



Baseline (µmol/L): DTG: 74.7 versus RAL: 75.2

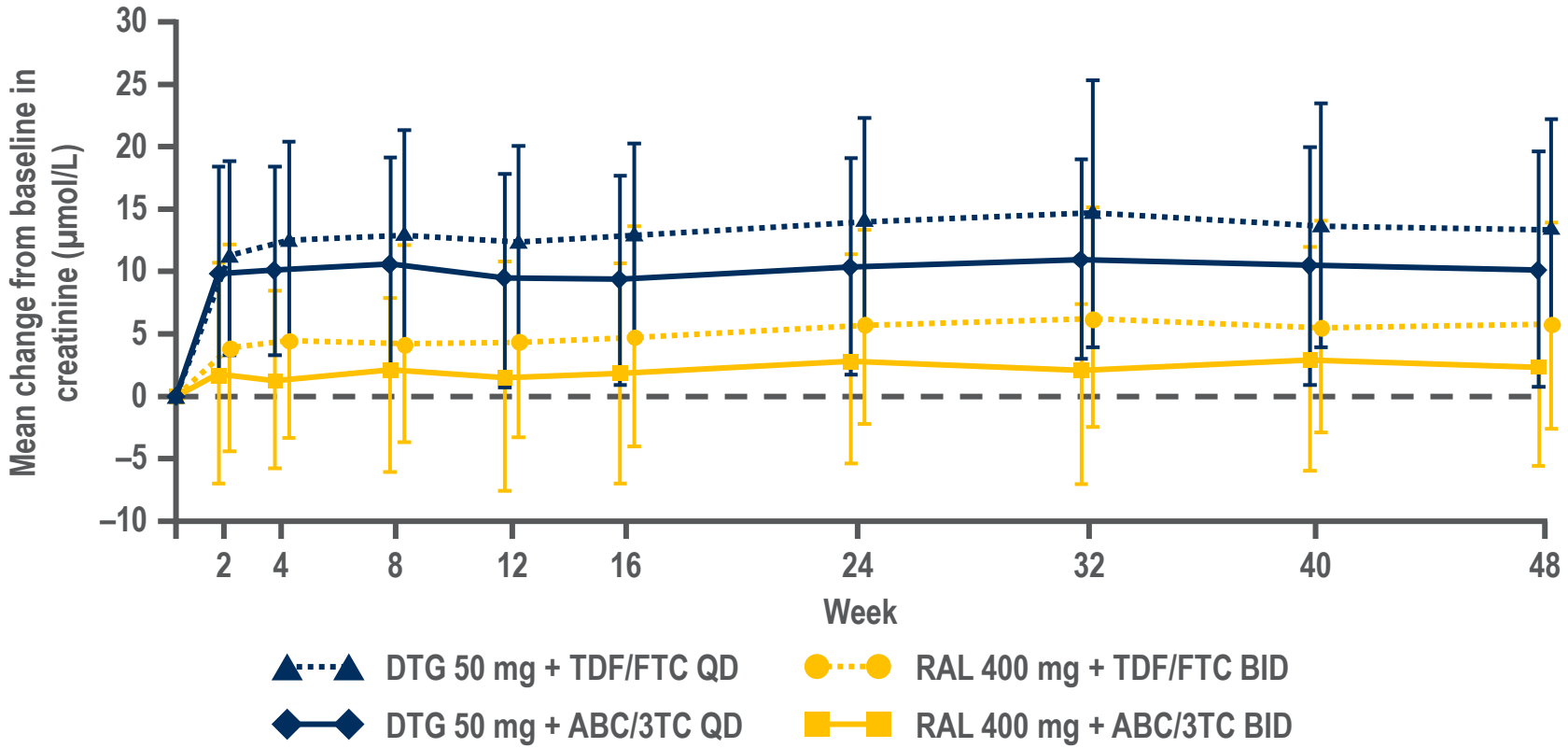
Creatinine clearance by Cockcroft-Gault, mean (SD)[4]	DTG 50 mg QD + NRTIs*		RAL 400 mg BID + NRTIs*	
	n	mL/min	n	mL/min
Baseline	411	125 (25.8)	411	127.8 (31.2)
Week 24	389	-17.5 (13.4)	384	-6.4 (13.8)
Week 48	369	-16.5 (14.2)	353	-5.4 (13.9)

A small initial increase in creatinine was observed with DTG, due to the blockade of creatinine secretion.[2,3] There was no further increase in mean serum CR from Week 48 to Week 96 (Week 0 to 96: DTG +14.6 mmol/L; RAL +8.2 mmol/L)[5]

*Mean change in serum CR (mg/dL): DTG, +0.14mg/dL, RAL, +0.05 mg/dL; based on conversion rate 0.011mg/dL = 1 µmol/L
CR, creatinine

1. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
2. Raffi F et al. IAS 2012. Abstract THLBB04
3. Raffi F et al. *Lancet* 2013;381:735–43
4. Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282
5. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

CHOICE OF BACKGROUND REGIMEN DID NOT INFLUENCE EFFECT OF DTG ON CREATININE LEVELS



Subjects receiving each NRTI background, n (%)	DTG	RAL
TDF/FTC	242 (59)	247 (60)
ABC/3TC	169 (41)	164 (40)

Curtis LD, et al. IAS 2013. Poster TUPE282

FEW REPORTS OF RENAL DYSFUNCTION, AND NONE ATTRIBUTED TO DTG

- There were few reports of renal dysfunction, and none were considered by the investigator to be related to DTG

Group	Gender	Age	Description	Related	Withdrawn
DTG	M	52	Pre-existing renal failure, diabetes, proteinuria. Creatinine small stable increase, increase in proteinuria before fall below baseline levels. Reported as chronic renal failure	N	N
DTG	M	38	On TDF/FTC. Fluctuating creatinine up to Grade 1	N	N
DTG	M	42	Increase in creatinine during vancomycin infusion for septic arthritis; subsequently returned to baseline	N	N

Curtis LD, et al. IAS 2013. Poster TUPE282

SPRING-2: SUMMARY

- DTG was non-inferior to RAL[1,2]
  - 88% vs 85% reached undetectability through 48 weeks (p=0.003)[1]
  - 81% vs 76% reached undetectability on RAL through 96 weeks[2]
- No INI or NRTI resistance through 96 weeks with DTG[2]
- DTG was effective regardless of baseline viral load
  - 82% of treatment-naive patients with HIV-1 RNA >100,000 copies/mL reached undetectability at Week 48[1]
  - 78% of treatment-naive patients with HIV-1 RNA >100,000 copies/mL reached undetectability at Week 96[2]
- DTG offered similar tolerability to RAL[2]
  - 2% vs 2% discontinued due to AEs at 48 weeks[2]
  - 2% vs 2% discontinued due to AEs at 96 weeks[2]

1. Raffi F et al. *Lancet* 2013;381:735–43
2. Adapted from Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35

ABBREVIATIONS

- 3TC, lamivudine
- ABC, abacavir
- AE, adverse event
- AST, aspartate amino transferase
- BID, twice daily
- BL, baseline
- c/mL, copies/mL
- CR, creatinine
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- FDA, Food and Drug Administration
- FTC, emtricitabine
- HDL, high density lipoprotein
- FDC, fixed-dose combination
- INI, integrase inhibitor
- IQR, inter quartile range
- LDL, low density lipoprotein
- NRTI, nucleoside reverse transcriptase inhibitor
- PDVF, protocol-defined virologic failure
- QD, once daily
- RAL, raltegravir
- SD, standard deviation
- TDF, tenofovir

Indication(s): Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents aged 12 years and older and weighing at least 40 kg.

Succinct safety information:

Contraindications: Coadministration with dofetilide. Hypersensitivity to dolutegravir or to any of the excipients. **Warnings and Precautions**: Integrase class resistance of particular concern: The decision to use dolutegravir in the presence of integrase class resistance should take into account that the activity of dolutegravir is considerably compromised for viral strains harbouring . Hypersensitivity reactions: Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dolutegravir and other suspect agents should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop. Immune Reactivation Syndrome: An inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Drug interactions: Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. Metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required. Osteonecrosis: Although the aetiology is considered to be multifactorial, cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. **Undesirable effects:** Very common: Headache, nausea, diarrhoea. Common: Insomnia, abnormal dreams, dizziness, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort, rash, pruritus, fatigue, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations, creatine phosphokinase (CPK) elevations.

Dosage and administration: 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). 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. Co-administration of Tivicay with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). 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. Method of administration: Oral use. Tivicay can be taken with or without food . In the presence of integrase class resistance, Tivicay should preferably be taken with food to enhance exposure (particularly in patients with Q148 mutations).

For full information please refer to MOH approved Prescribing Information