Tivicay (dolutegravir) 50 mg tablets

gsk ViiV Healthcare

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

SAILING

Efficacy and safety of dolutegravir (DTG) in treatment-experienced INI-naïve patients

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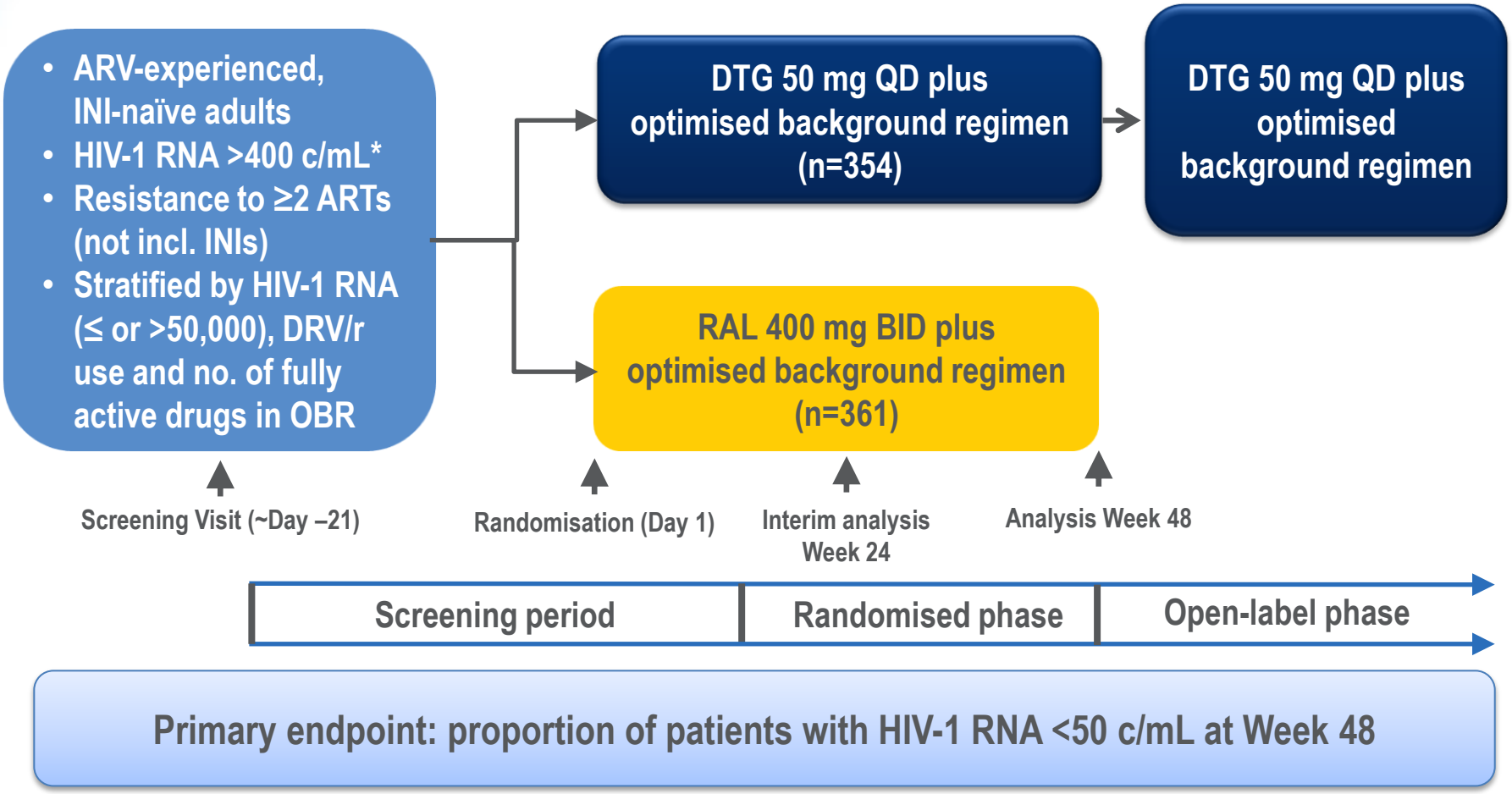
DTG TRIALS IN TREATMENT-EXPERIENCED ADULT SUBJECTS WITH HIV

SAILING[1] **INI-naïve**	N=715	Phase III, randomised, double-blind, active-controlled, parallel group, non-inferiority, multicentre study of: • DTG (50 mg QD) + ART • RAL (400 mg BID) + ART
VIKING[2] **(Cohort I)** **INI-resistant**	N=27	Phase IIb open-label, single-arm multicentre study (Cohort I) of: • DTG 50 mg QD + OBR (not incl. RAL)
VIKING[2] **(Cohort II)** **INI-resistant**	N=24	Phase IIb open-label, single arm multicentre study (Cohort II) of: • DTG (50 mg BID) + OBR (not incl. RAL) • subjects required to have ≥1 fully active ARV for Day 11 optimisation (not required for Cohort I)
VIKING-3[3] **INI-resistant**	N=183	Phase III, open-label, single-arm, multicentre study of: • DTG (50 mg BID) + OBR (not incl. RAL)

BID, twice daily; QD, once daily; OBR, optimised background regimen

1. Cahn P, et al. *Lancet* 2013;382(9893):700-708
2. Eron JJ, et al. *J Infect Dis* 2013;207:740–8
3. Nichols G, et al. IAS 2013. Poster TULBPE19

SAILING: STUDY DESIGN



*With 2 consecutive HIV-1 RNA ≥400 c/mL, unless screening HIV-1 RNA >1,000 c/mL

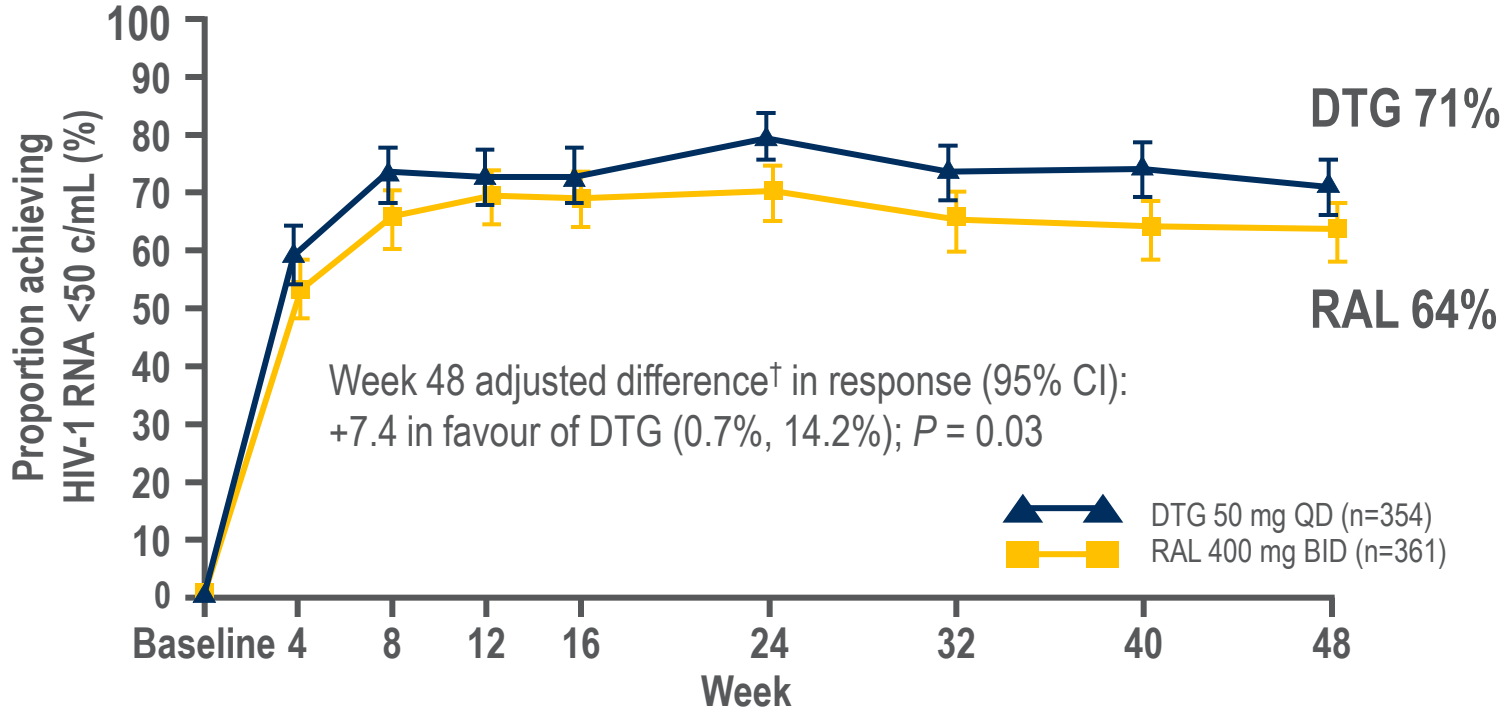
Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
Pozniak A, et al. CROI 2013. Abstract 179LB

BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
Age, median (years)	42	43
Gender, female (%)	30	34
Race		
White (%)	49	48
African American or African heritage (%)	40	44
HIV-1 RNA, median (log_{10} c/mL)	4.17	4.21
>50,000 c/mL (%)	30	30
CD4+ count, median (cells/mm^3)	205	193
HBV coinfection (%)	5	4
HCV coinfection (%)	9	13
Duration prior ART, median (months)	80	72
≥3 class resistance (%)	47	51
Most common background regimens, n (%)		
DRV/r, TDF	62 (18)	73 (20)
LPV/r, TDF	40 (11)	40 (11)
DRV/r, ETR	33 (9)	40 (11)
LPV/r	36 (10)	35 (10)
ATV/r, TDF	37 (10)	33 (9)
DRV/r, MVC	23 (6)	19 (5)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

IN TREATMENT-EXPERIENCED, INI-NAÏVE PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS RAL



DTG mg QD was statistically superior to RAL 400 mg BID based on a pre-specified snapshot analysis* (HIV-1 RNA <50 copies / mL) at Week 48 (*P* = 0.03)

Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm^3; RAL: +153 (144) cells/mm^3

*Analysis based on all subjects randomised who received ≥1 dose of study drug, excluding four subjects at one site with violations of good clinical practice; SD, standard deviation

†Adjusted difference based on stratified analysis adjusting for BL HIV-1 RNA (≤50,000 c/mL vs >50,000 c/mL), DRV/r use without primary PI mutations and baseline PSS (2 vs <2)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

FEWER VIROLOGIC NON-RESPONDERS FOR DTG VS. RAL (SNAPSHOT)

n/N (%)	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
HIV-1 RNA <50 c/mL, n (%)	251 (71)	230 (64)
Virologic non-responder[a]	71 (20)	100 (28)
No virologic data at Week 48[b]	32 (9)	31 (9)
Per protocol, HIV-1 RNA <50 c/mL	238/325 (73)	225/340 (66)
Adjusted difference, % (95% confidence interval)	7.5% (0.6, 14.3)	
Response <50 c/mL by baseline HIV-1 RNA		
≤50,000 c/mL	186/249 (75)	180/254 (71)
>50,000 c/mL	65/105 (62)	50/107 (47)
Response <50 c/mL by background regimen phenotypic susceptibility score[c]		
<2	70/104 (67)	61/94 (65)
2	181/250 (72)	169/267 (63)
Use of DRV without primary PI mutations		
Yes	50/72 (69)	54/77 (70)
No	201/282 (71)	176/284 (62)

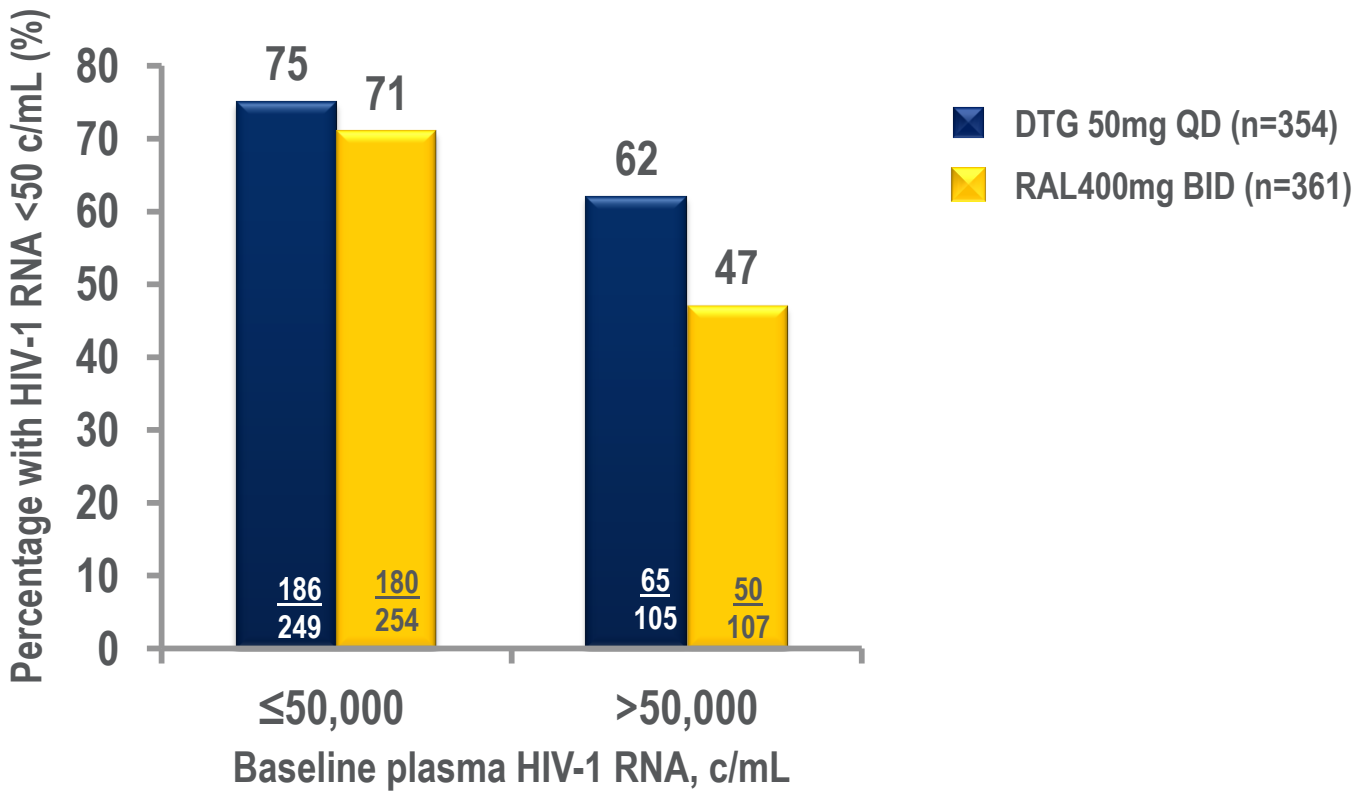
[a] HIV-1 RNA not <50 c/mL in window; discontinued for lack of efficacy; discontinued for other reason while not <50 c/mL; change in ART

[b] Discontinued due to AE, death or for other reasons unrelated to safety; missing data but still on study

[c] Two subjects with PSS=3 were included in the score=2 category.

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD



- 30% of patients had baseline viral load >50,000 copies/mL

Adapted from Cahn P, et al. Lancet 2013;382(9893):700-708

DTG HAD FEWER RESISTANCE MUTATIONS THAN RAL THROUGH 48 WEEKS

The proportion of subjects with evidence of INI resistance was significantly lower in the DTG arm than in the RAL arm

	DTG 50 mg QD + OBR (n=354)	RAL 400 mg BID + OBR (n=361)
Protocol-defined virologic failure, n (%)	**21 (6)**	**45 (12)**
INI mutations*, n (%)	4(1)†	17 (5)‡

* Adjusted difference: -3.7% (95% CI:-6.1%,-1.2%); *P*=0.003. As the upper end of the 95% CI for the adjusted treatment difference was greater than 0, this finding demonstrated a statistically significant difference in favour of DTG.

† Treatment-emergent INI mutations detected: R263K, R263R/K, V151V/I; one patient developed a T97A and E138T/A mutation, however this patient was subsequently found to have a Q148 mutation at baseline.

‡One patient in each group had INI resistance at baseline

Substitutions seen at positions R263 and V151 did not confer high levels of resistance to DTG (2<fold change in IC50), or cross resistance to RAL.

Cahn P, et al. *Lancet* 2013;382(9893):700-708

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708 (appendix)

DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS

Adverse Events (AE), n (%) at 48 weeks	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
Subjects with AEs leading to discontinuation, n (%)	4 (1)	11 (3)
Serious drug-related AEs	2 (1)	4 (1)
Fatal AEs	0	3 (1)

Low rate of discontinuation due to AEs at 48 weeks (1% for DTG and 3% for RAL)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

DTG OFFERED SIMILAR TOLERABILITY TO RAL THROUGH 48 WEEKS

AEs, n (%)	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
AEs (≥5% in either arm)		
Diarrhoea	71 (20)	64 (18)
Upper respiratory tract infection	38 (11)	29 (8)
Headache	33 (9)	31 (9)
Nausea	29 (8)	29 (8)
Cough	33 (9)	24 (7)
Influenza	24 (7)	26 (7)
Nasopharyngitis	23 (6)	22 (6)
Urinary tract infection	26 (7)	18 (5)
Vomiting	20 (6)	20 (6)
Fatigue	15 (4)	24 (7)
Rash	19 (5)	18 (5)
Arthralgia	10 (3)	18 (5)
Upper abdominal pain	17 (5)	5 (1)

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

DTG WAS WELL TOLERATED[1]

	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
ALT	9 (3%)	7 (2%)
Cholesterol	6 (2%)	14 (4%)
Creatinine*	1 (<1%)	1 (<1%)
Hyperglycaemia	4 (1%)	7 (2%)
Lipase	4 (1%)	7 (2%)
Total bilirubin**	21 (6%)	14 (4%)
CPK	7 (2%)	4 (1%)

* As previously described, small non-progressive increase in serum creatinine due to OCT2 inhibition[2]

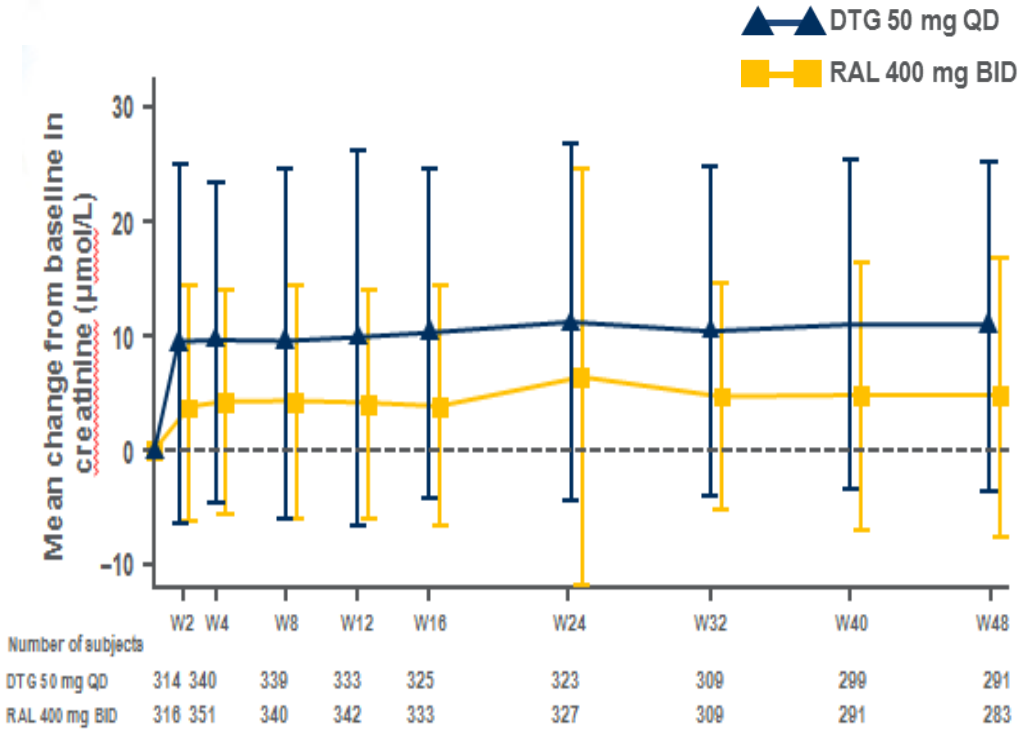
** 16/21 subjects in the DTG arm and 11/14 in the RAL arm were receiving ATV[1]

ALT, alanine aminotransferase; CPK, creatine phosphokinase

1. Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
2. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred initially and then remained stable through 48 weeks.[1] These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.[2]



	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
Renal laboratory values[3]		
Change from baseline serum creatinine (µmol/L), mean (SD)	11.1 (15.53)* (n=291)	5.1 (12.23) (n=283)
Change from baseline urine albumin/creatinine ratio (mg/mmol), mean (SD)	-0.33 (27.51) (n= 260)	-0.56 (31.81) (n=253)

*As previously described, small non-progressive increase in serum creatinine due to OCT2 inhibition

ALT, alanine aminotransferase; CPK, creatine phosphokinase

1. Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708
2. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
3. Adapted from Cahn P, et al. IAS 2013. Abstract WELBB03

SUMMARY

In the Week 48 primary analysis, DTG 50 mg QD was statistically superior to RAL BID in proportion of subjects achieving HIV-1 RNA <50 c/mL

- In treatment experienced, INI-naïve subjects, DTG had statistically superior efficacy vs RAL
  - 71% vs 64% reached undetectability at Week 48 (*P*=0.03)
- DTG was effective regardless of baseline viral load
  - 62% of treatment-experienced patients with HIV-1 RNA>50,000 copies/mL reached undetectability
- Differences driven by lower rate of virologic failure in subjects on DTG
  - Proportion of subjects with evidence of INI resistance was significantly lower in DTG arm
  - Treatment-emergent resistance to background regimen was also statistically lower in DTG arm
- DTG 50 mg QD was well tolerated and offered similar tolerability to RAL
  - 1% vs 3% discontinued due to AEs

Cahn P, et al. *Lancet* 2013;382(9893):700-708

ABBREVIATIONS

- AE, adverse event
- ART, antiretroviral therapy
- ARV, antiretroviral
- ATV/r, atazanavir/ritonavir
- BID, twice daily
- c/mL, copies/mL
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- ETR, etravirine
- HBV, hepatitis B virus
- HCV, hepatitis C virus
- HIV, Human immunodeficiency virus
- INI, integrase inhibitor
- LPV/r, lopinavir/ritonavir
- MVC, maraviroc
- OBR, optimised background regimen
- PDVF, protocol-defined virologic failure
- RAL, raltegravir
- RNA, ribonucleic acid
- TDF, tenofovir
- mITT-E, modified intent-to-treat exposed analysis
- QD, once daily

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