Tivicay (dolutegravir) 50 mg tablets

gsk ViiV Healthcare

WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

FLAMINGO

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

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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 (800/100 mg QD) + 2 NRTIs

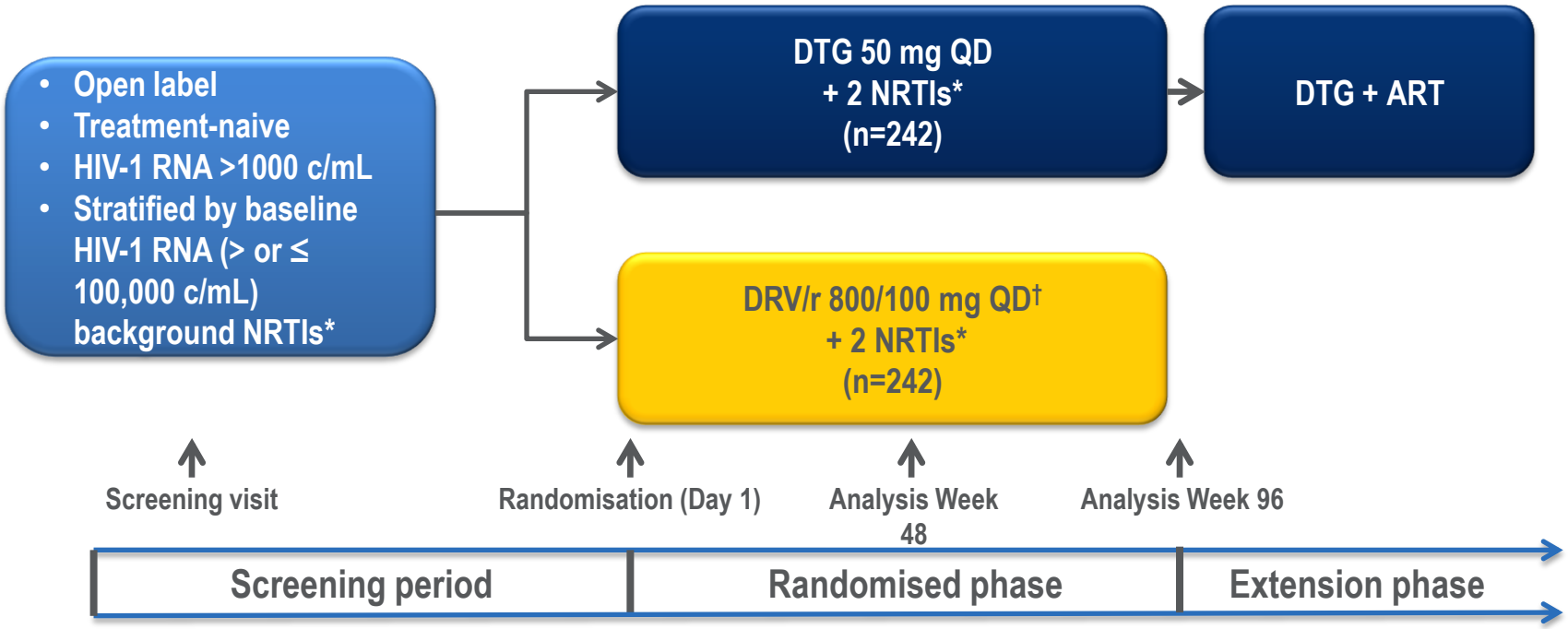
SPRING-2[3,4] — N=822

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

FLAMINGO: ONGOING PHASE III TRIAL IN TREATMENT-NAÏVE SUBJECTS WITH HIV



Primary endpoint: Proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot) with non-inferiority margin of -12%

*Stratified by HIV-1 RNA >100,000 or ≤100,000 c/mL and ABC/3TC or TDF/FTC

† Given as 2 x 400 mg tablets

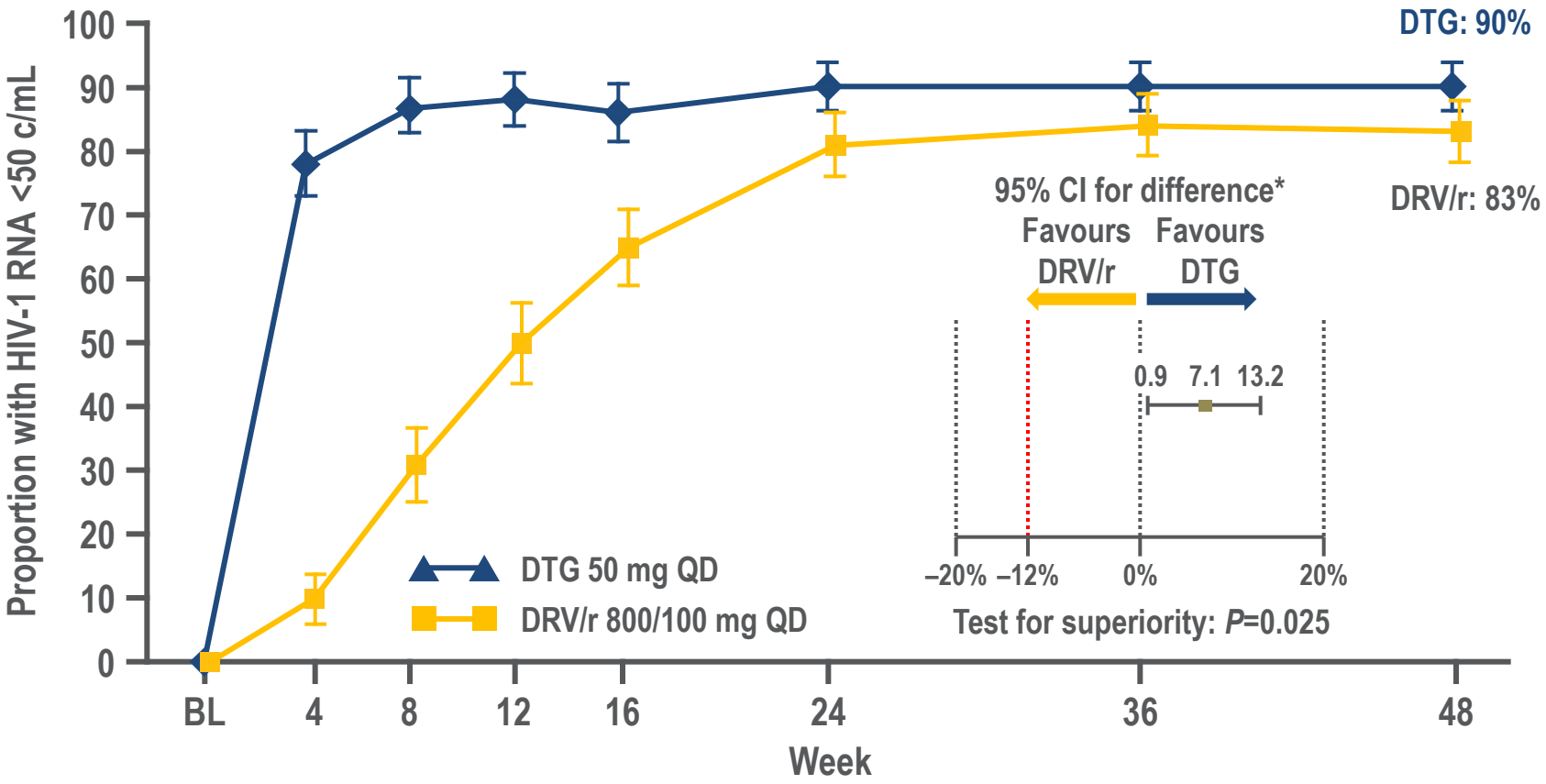
Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)	Total (N=484)
Age (years), median	34	34	34
Female, %	13	17	15
African American/African heritage, %	25	22	23
HBV/HCV positive, %	4/7	2/7	3/7
CDC class C, %	4	2	3
HIV-1 RNA (log_{10} c/mL), median	4.49	4.48	4.49
>100,000 c/mL, %	25	25	25
CD4+ (cells/mm^3), median	390	400	395
<50, %	2	2	2
50 to <200, %	8	8	8
200 to <350, %	30	21	26
350 to <500, %	33	38	36
≥500, %	27	31	29
Investigator-selected ABC/3TC, %	33	33	33

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

IN TREATMENT-NAIVE SUBJECTS PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS DRV/r



- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy

Week 48 snapshot analysis

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

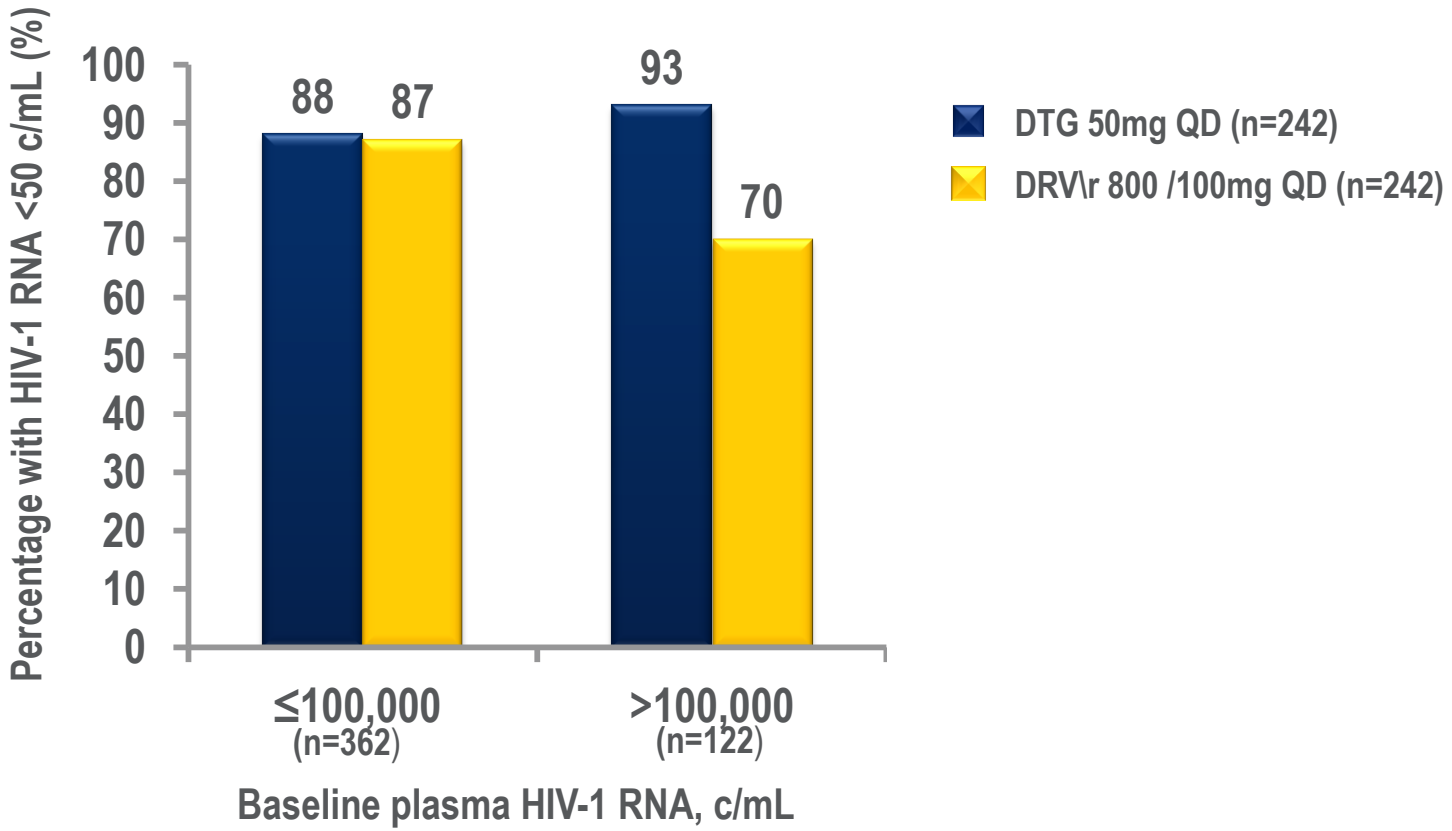
DTG HAD A STATISTICALLY SUPERIOR VIROLOGIC RESPONSE VERSUS DRV/r THERAPY AT WEEK 48

Outcome (Snapshot) at Week 48, n (%)	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Virologic success (HIV-1 RNA <50 c/mL)	**217 (90%)**	**200 (83%)**
Virologic non-response	**15 (6%)**	**18 (7%)**
Data in window not <50 c/mL	6 (2%)	11 (5%)
Discontinued for lack of efficacy	1 (<1%)	1 (<1%)
Discontinued for other reason while not <50 c/mL	3 (1%)	5 (2%)
Change in ART	5 (2%)	1 (<1%)
No Week 48 virologic data	**10 (4%)**	**24 (10%)**
Discontinued due to AE or death	3 (1%)	9 (4%)
Discontinued for other reasons	6 (2%)	11 (5%)
Missing data during window but on study	1 (<1%)	4 (2%)

Week 48 snapshot analysis

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

DTG WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD

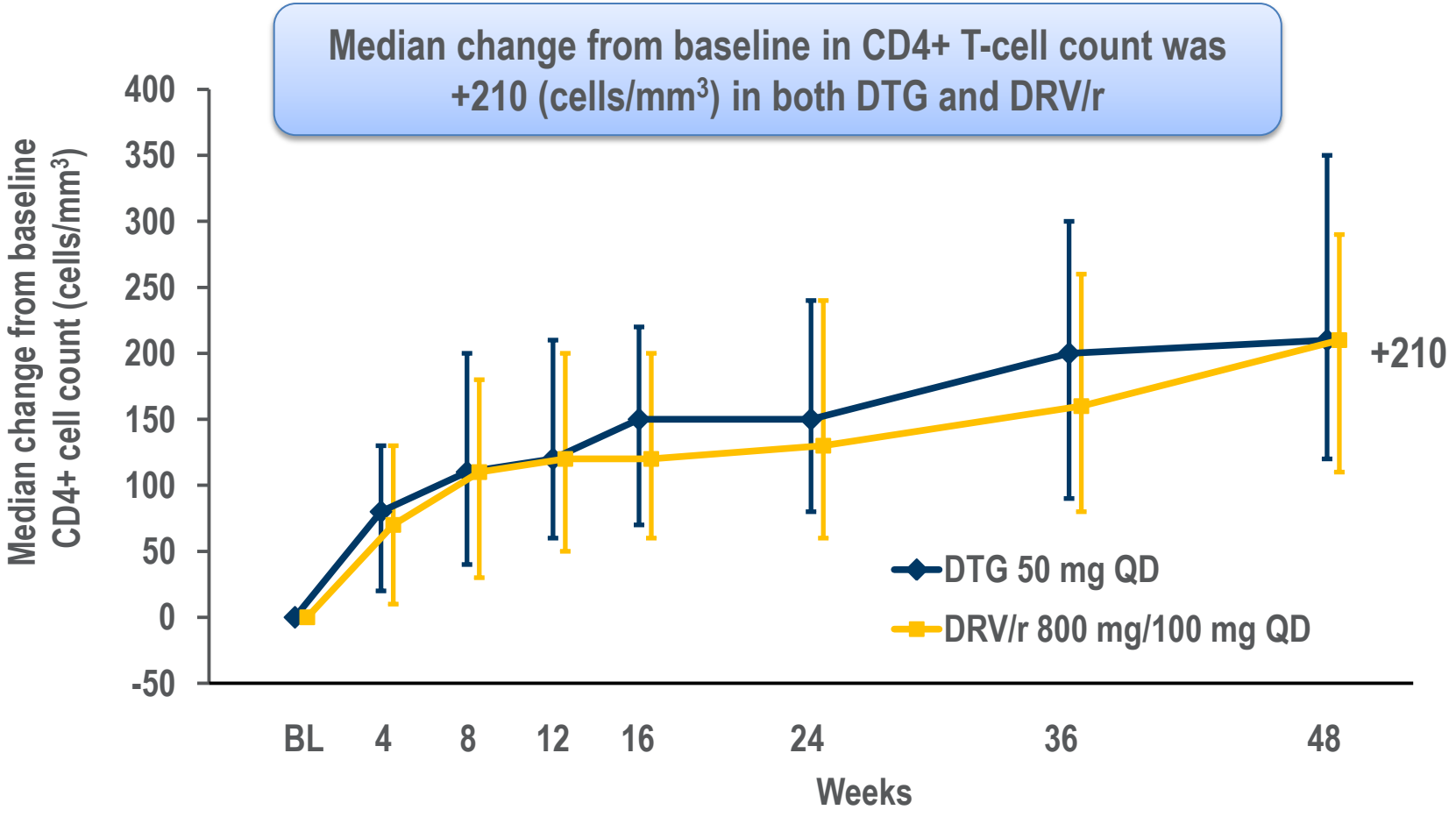


- 25% of treatment-naïve patients had a baseline viral load >100,000 copies/mL

Week 48 snapshot analysis

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

PROVEN CD4+ T-CELL RESPONSE



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NO EMERGENT INI, NRTI OR PI MUTATIONS THROUGH 48 WEEKS WITH DTG

No treatment-emergent major INI, NRTI or PI resistance mutations were observed through 48 weeks in either DTG or DRV/r

	DTG 50 mg QD	DRV/r 800/100 mg QD
Protocol-defined virologic failure, n (%)	**2 (<1)**	**2 (<1)**
INI mutations, n	0	0
NRTI mutations, n	0	0
PI mutations, n	0*	0

PDVF was defined as 2 consecutive HIV-1 RNA values >200 c/mL, on or after Week 24
*One subject in the DTG treatment group had phenotypic resistance to nelfinavir. This subject had secondary PI resistance mutations L10V, I13V, K20R, E35D, M36I, I62I/V, L63T and L89M at baseline and at PDVF

PDVF, protocol-defined virologic failure

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS THROUGH 48 WEEKS

DTG was well tolerated with lower rates of diarrhoea vs darunavir / r

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Overall, n (%)	**206 (85)**	**205 (85)**
Common AEs (≥10% in either arm)		
Diarrhoea	41 (17)	70 (29)
Nausea	39 (16)	43 (18)
Headache	37 (15)	24 (10)
Discontinuations due to AE/ stopping criteria met	**4 (2)**	**10 (4)**
Drug-related Grade 2–4	**23 (10)**	**30 (12)**
Serious – any event*	**26 (11)**	**13 (5)**
Serious drug-related – any event	**1 (<1)†**	**0**
Fatal AEs	**0**	**0**

*Each individual SAE was reported in <1% of subjects in each treatment group

†DTG + ABC/3TC: 1 suicide attempt (subject with a history of suicidality)

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

DTG WAS WELL TOLERATED WITH FEW DISCONTINUATIONS

Discontinuations due to AEs at 48 weeks were 2% for DTG and 4% for DRV/r

	DTG 50 mg QD (n=242)	DRV/r 800 mg/100 mg QD (n=242)
Individuals with events leading to discontinuation, n (%)	**4 (2)**	**10 (4)**
System organ class (>1 event in either arm)		
Gastrointestinal disorders	2 (<1)	2 (<1)
Nervous system disorders	2 (<1)	2 (<1)
General disorders and administration site conditions	0	2 (<1)
Abnormal transaminase	0	2 (<1)
Skin and subcutaneous tissue disorders	0	2 (<1)

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DTG WAS WELL TOLERATED

Maximum post-baseline emergent toxicity Grade 3–4, n (%)	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Cholesterol	0	3 (1)
LDL cholesterol	2 (<1)	6 (2)
ALT	3 (1)	4 (2)
Creatine kinase	16 (7)	9 (4)
Creatinine	0	0

- Small (0.1–0.2 mg/dL) non-progressive increases in serum creatinine were observed in the DTG arm due to inhibition of OCT2
- Mean change from baseline in fasting LDL cholesterol was significantly lower for DTG vs. DRV/r (3.1 mg/dL vs 14.1 mg/dL, *P*<0.001) (pre-specified)
- Significantly fewer Grade ≥2 LDL values on DTG (2% vs 7%, *P*<0.001) (pre-specified)

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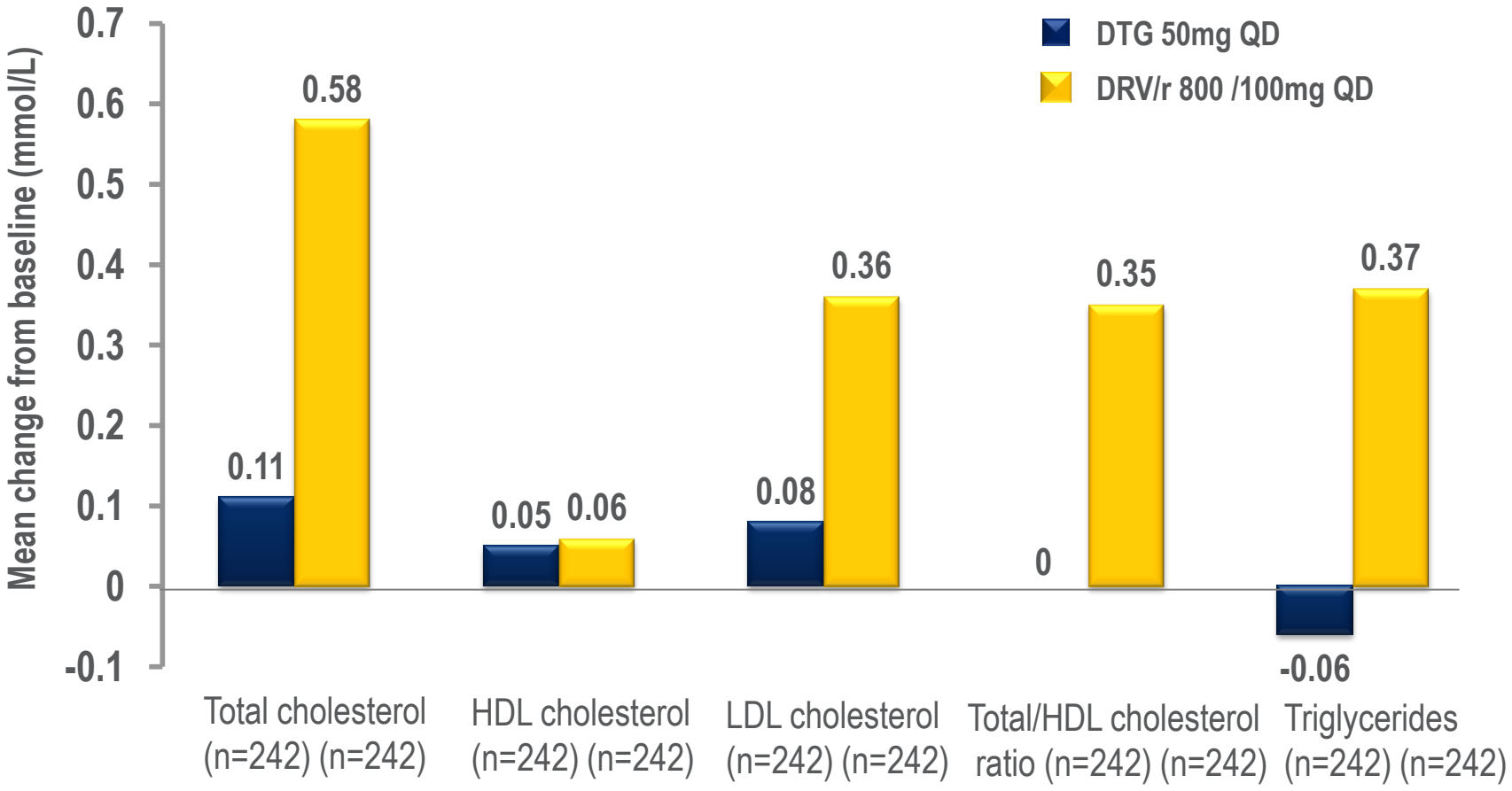
AT 48 WEEKS DTG HAD A FAVOURABLE LIPID PROFILE VS DRV/r



Data on file. UK/DLG/0024/13, 01/11/13

FLAMINGO: SUMMARY

- In treatment-naïve patients, DTG had statistically superior efficacy vs darunavir / r
  - 90% vs 83% reached undetectability at Week 48 (*P*=0.025)
- DTG was effective regardless of baseline viral load
  - 93% of treatment-naïve patients with HIV-1 RNA >100,000 copies. mL reached undetectability
- No emergent primary INI, PI or NRTI mutations were seen in either arm
- DTG was generally well tolerated with lower rates of diarrhoea vs darunavir / r
  - 2% vs 4% discontinued due to AEs at 48 weeks

Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

ABBREVIATIONS

- 3TC, lamivudine
- ABC, abacavir
- AE, adverse event
- ART, antiretroviral therapy
- BID, twice daily
- c/mL, copies/mL
- CMH
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- FC, fold change
- FDC, fixed-dose combination
- FTC, emtricitabine
- HIV, Human immunodeficiency virus
- INI, integrase inhibitor
- IQR, interquartile range
- MDSF
- NRTI, nucleoside reverse transcriptase inhibitor
- PDVF, protocol defined virologic failure
- PI, protease inhibitor
- RAL, raltegravir
- RNA, ribonucleic acid
- 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