SINGLE

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

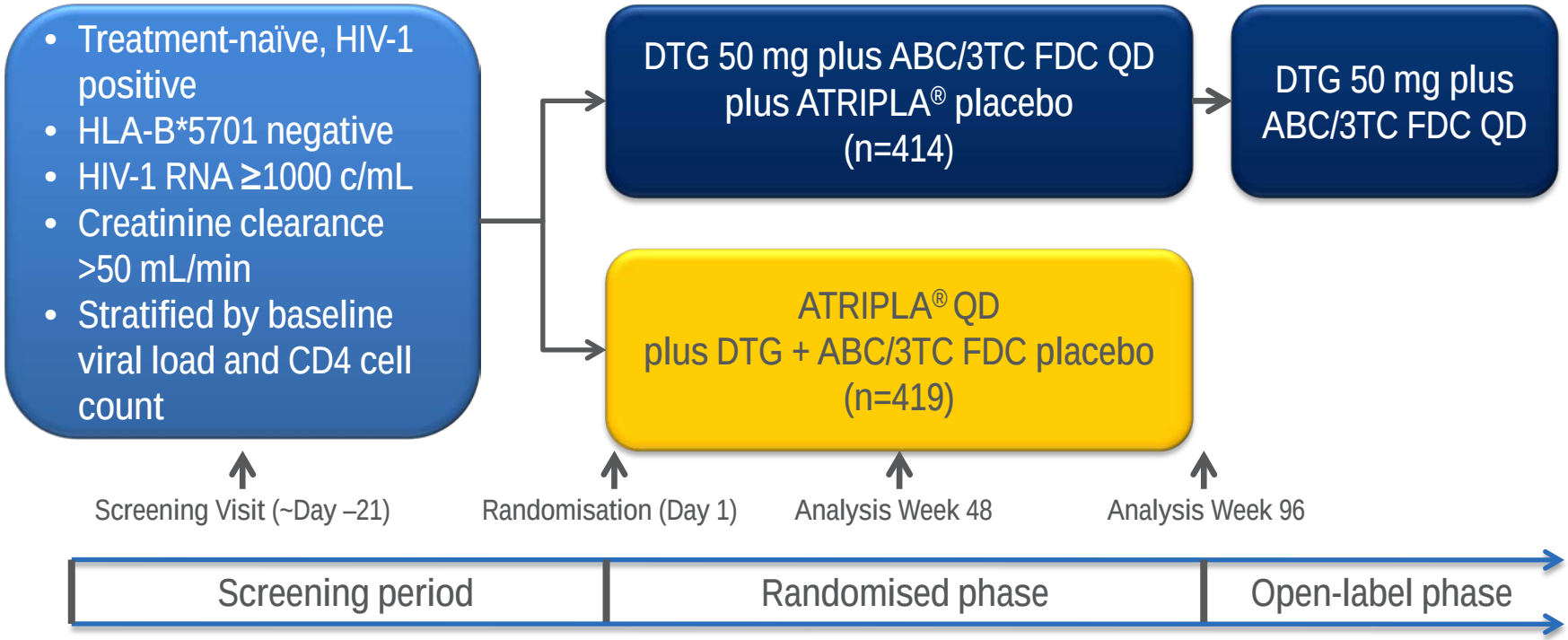
PHASE III DTG TRIALS IN TREATMENT-NAÏVE ADULT SUBJECTS WITH HIV

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

SINGLE STUDY DESIGN



Primary endpoint: Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis (-10% non-inferiority margin with pre-specified tests for superiority)

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

BASELINE CHARACTERISTICS

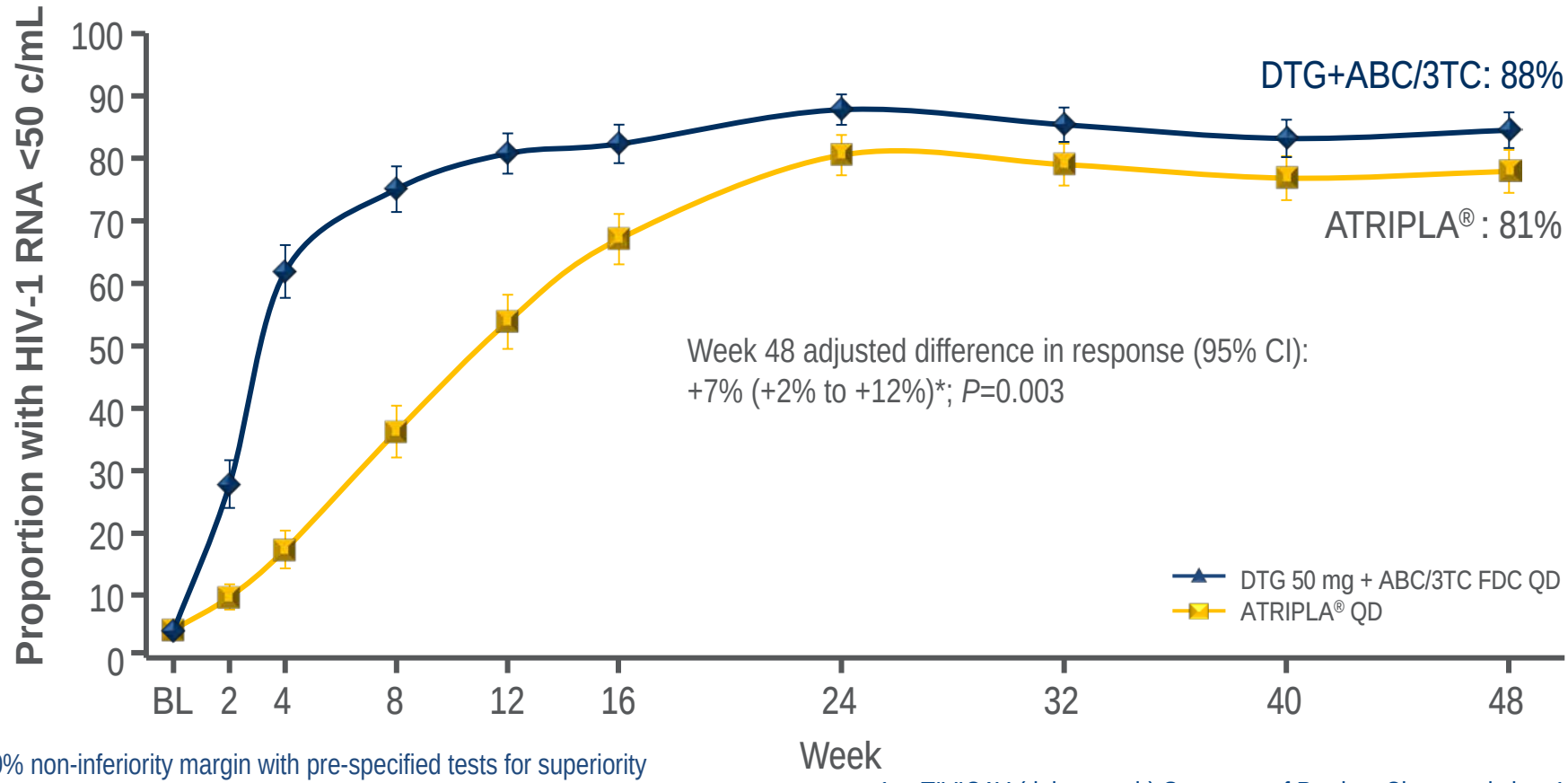
Characteristic	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Median age, years	36	35
Female, %	16	15
African American / African Heritage, %	24	24
CDC class C, %	4	4
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.7	4.7
>100,000 c/mL, %	32	31
Median CD4 cell count, cells/mm^3	335	339
<200, %	14	14
200 to <350, %	39	38
350 to <500, %	32	31
≥500, %	15	17

CDC, Centers for Disease Control

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (appendix)

IN TREATMENT-NAÏVE PATIENTS, DTG + ABC/3TC HAD STATISTICALLY SUPERIOR EFFICACY VS ATRIPLA®

DTG was statistically superior to Atripla® at Week 48
Subjects receiving DTG achieved faster virologic suppression than Atripla® (*P*<0.0001)*[1]



*-10% non-inferiority margin with pre-specified tests for superiority

1. TIVICAY (dolutegravir) Summary of Product Characteristics, 11/2013
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

VIROLOGIC RESPONSE OUTCOMES WITH DTG + ABC/3TC STATISTICALLY SUPERIOR TO ATRIPLA® AT WEEK 48

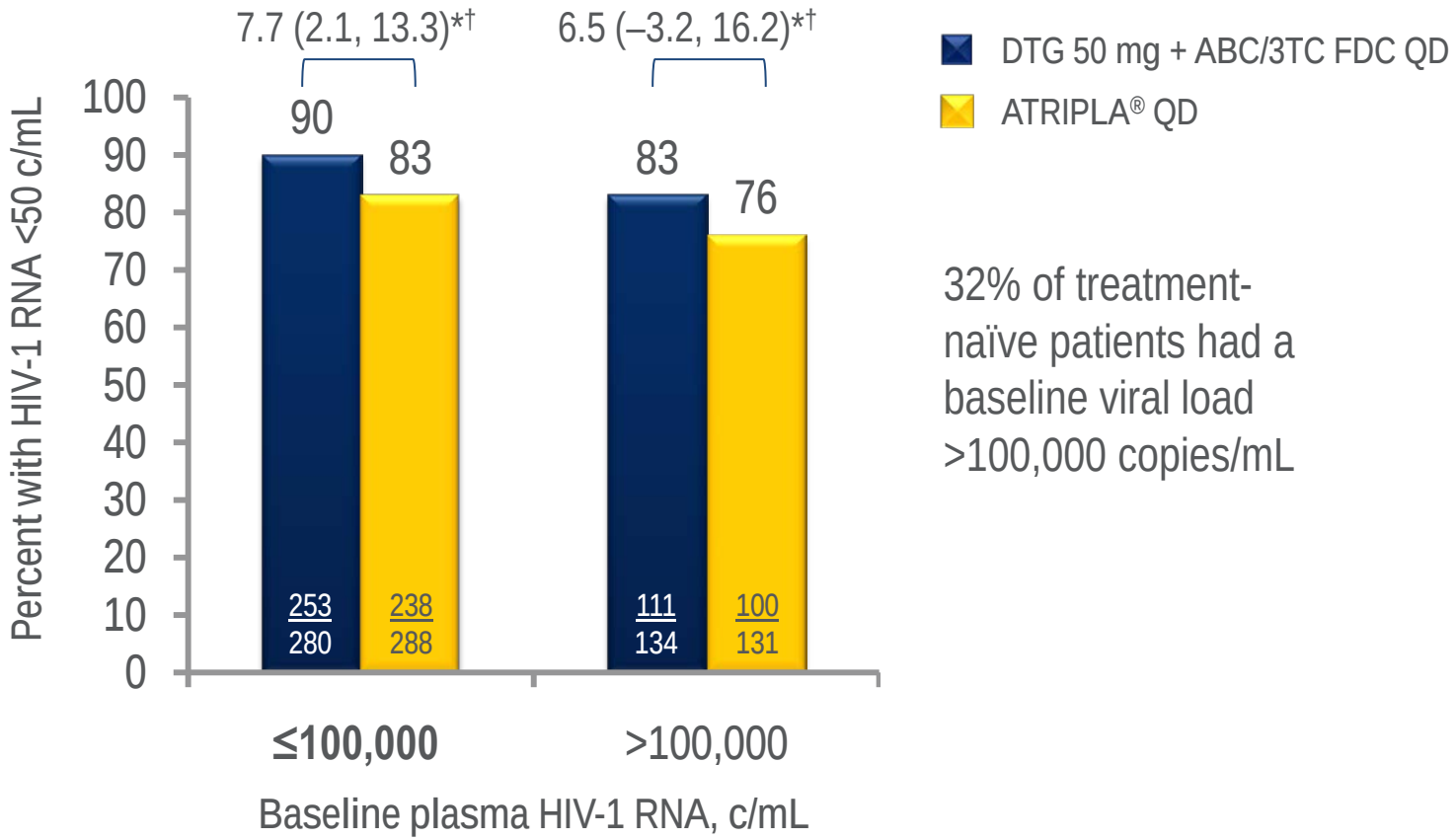
Outcome (Snapshot) at Week 48, n (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Virologic success	364 (88)	338 (81)
Virologic non response	21 (5)	26 (6)
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not <50 c/mL	8 (2)	12 (3)
No virologic data at Week 48	29 (7)	55 (13)
Discontinued because of AE or death*	9 (2)	40 (10)
Discontinued for other reasons	20 (5)	14 (3)
Missing data during window, but on study	0	1 (<1)

*Deaths: n=2, both on Atripla®: n=1 primary cause of death (sepsis) judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla®; n=1 not related to Atripla® (pneumonia)

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b
Data on file. SINGLE STUDY. UK/DLG/0027/13. November 2013

DTG + ABC/3TC WAS EFFECTIVE REGARDLESS OF BASELINE VIRAL LOAD

At Week 48, the number of patients achieving virologic response was numerically higher in the DTG + ABC/3TC group vs the Atripla® group, regardless of baseline viral load

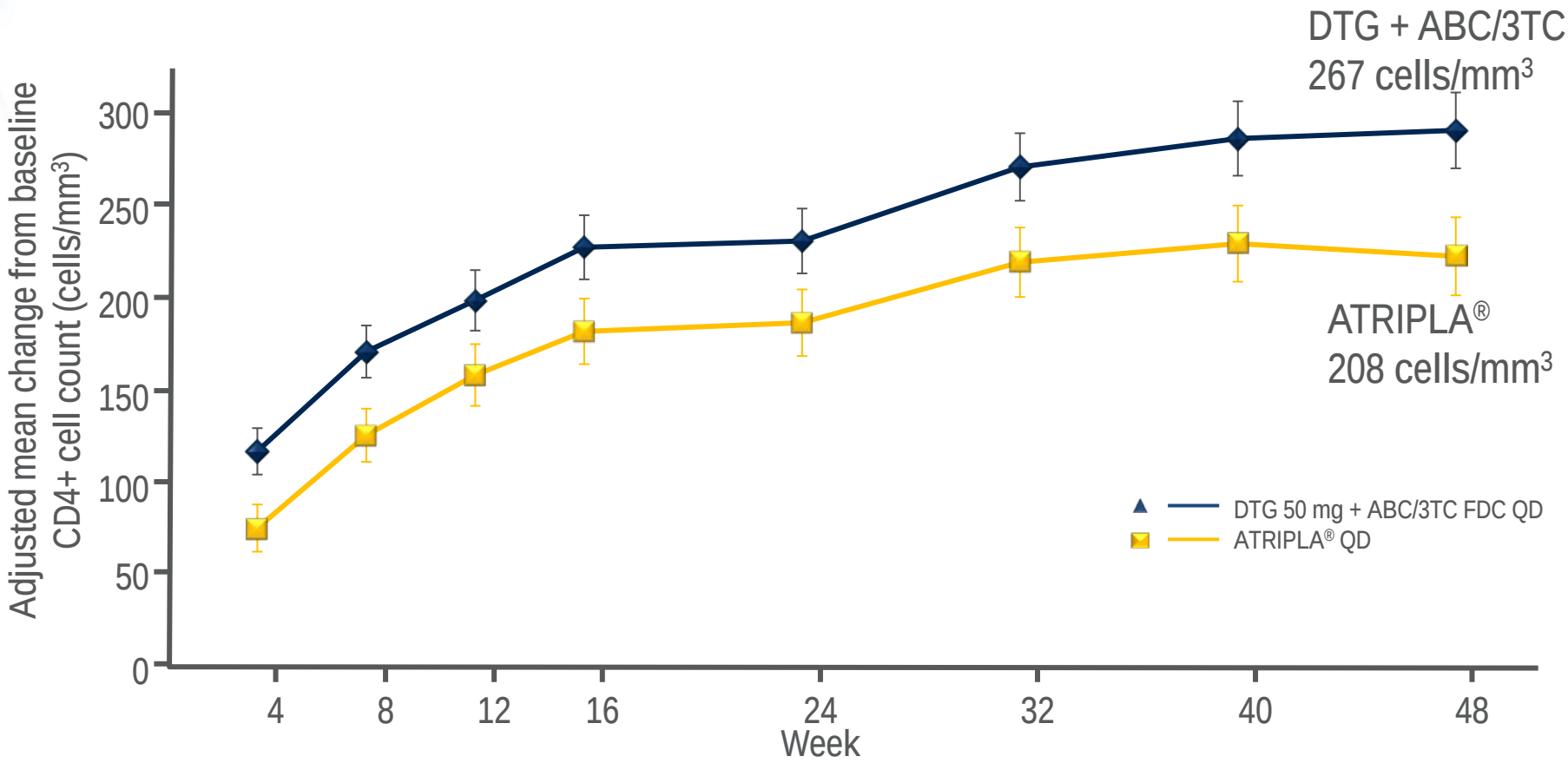


32% of treatment-naïve patients had a baseline viral load >100,000 copies/mL

*P=0.831; †test for homogeneity; p value confirms that there is no evidence of heterogeneity in treatment difference across the baseline stratification factors

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

DTG + ABC/3TC HAD STATISTICALLY SUPERIOR CD4+ T-CELL INCREASES VS ATRIPLA® AT WEEK 48



Week 48 difference in response (95% CI): 59 (33 to 84); $P < 0.001$[2]

Significant at pre-specified level of 4%[2]

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG

Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48[1]

	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects with PDVF	18 (4%)	17 (4%)
PDVF genotypic population[2]	11	9
NRTI major mutations	0	1(K65K/R)
Integrase-resistant major substitution	0†	0
NNRTI major mutations	0	4 (K101E, K103N or K103K/N, G190G/A)*

PDVF was defined as two consecutive plasma HIV-1 RNA values of ≥50 c/mL between weeks 24 and 48

*n=1 with K101E, n=1 with K103K/N, n=1 with G190G/A and n=1 with K103N+G190G/A

†E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b
3. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (suppl appendix)

DTG + ABC/3TC WAS BETTER TOLERATED VS ATRIPLA® WITH FEWER DISCONTINUATIONS

Discontinuations due to AEs were 2% for DTG + ABC/3TC vs 10% for Atripla® at week 48[1]

AEs, n (%)	DTG 50 mg +ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects with AEs leading to withdrawal, n (%)	10 (2)	42 (10)
Serious drug-related AE	1 (<1)*	8 (2)†
Fatal AEs	0	2 (<1)‡

Drug-related Grade 2 to 4 AEs (any event) were 13% (53/414) for DTG + ABC/3TC and 27% (114/419) for Atripla®[2]

*DTG+ABC/3TC: 1 drug hypersensitivity; †Atripla®: 4 psychiatric, 2 hypersensitivity reaction, 1 cerebral vascular accident, 1 renal failure; ‡Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla®, n=1 not related to Atripla® (pneumonia).

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Data on file. UK/DLG/0026/13,01/11/13

DTG + ABC/3TC WAS BETTER TOLERATED VS ATRIPLA®

RATES OF MOST COMMON AEs (ALL GRADES ≥10% IN EITHER REGIMEN)

DTG HAD A LOWER IMPACT ON LIVER CHEMISTRY THAN ATRIPLA®

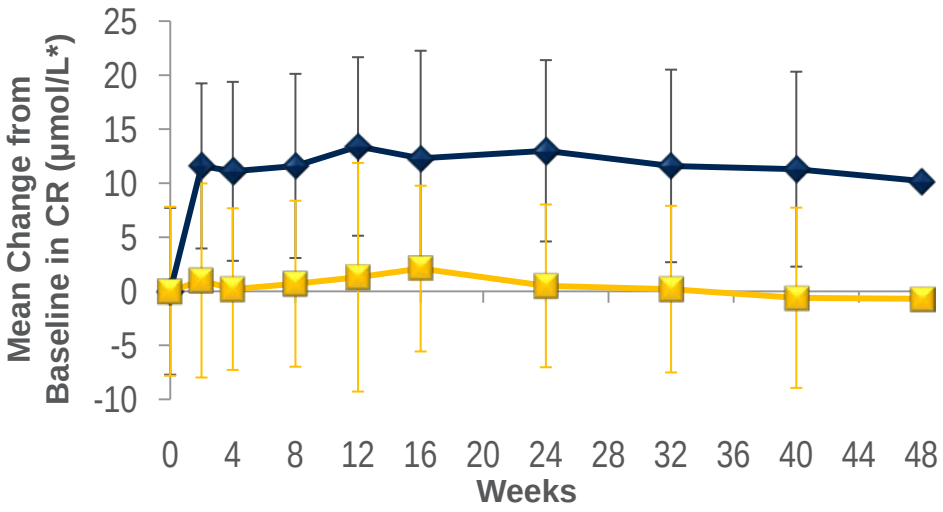
Parameter/Criteria, (%)	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Subjects meeting ≥1 FDA stopping criteria	10 (2)	39 (9)
ALT ≥20xULN	0	0
ALT ≥5xULN	1 (<1)	2 (<1)
ALT ≥3xULN	5 (1)	15 (4)
Total bilirubin >1.5xULN	3 (<1)	2 (<1)
Alkaline phosphatase >1.5xULN	1 (<1)	19 (5)
ALT and/or AST >3xULN and total bilirubin >1.5xULN	0	0

ULN, upper limit of normal

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

THE EFFECT OF DTG ON SERUM CREATININE IS NOT CLINICALLY RELEVANT

Small increases in serum creatinine occurred in the first week and remained stable through 48 weeks.[1,2] These changes are not considered to be clinically relevant as the glomerular filtration rate is unchanged.[3]



Creatinine clearance by Cockcroft-Gault, mean (SD)[4]	DTG 50 mg + ABC/3TC QD		ATRIPLA® QD	
	n	mL/min	n	mL/min
Baseline	414	129.7 (36.4)	419	130.5 (30.8)
Week 24	384	-18.2 (15.0)	362	-1.2 (14.6)
Week 48	366	-13.1 (15.6)	339	2.1 (15.7)

Urine albumin/creatinine (mg/mmol CR)[1]	DTG 50 mg+ABC/3TC QD	ATRIPLA® QD
Median change (IQR) from baseline to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

*10 µmol/L=0.11mg/dL[5]

1. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. TIVICAY (dolutegravir) Summary of Product Characteristics, 11/2013
3. Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996
4. Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282
5. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

RENAL ADVERSE EVENTS WERE RARELY REPORTED AND NONE WERE ATTRIBUTED TO DTG

Group	Gender	Age	Description	Related	Withdrawn
DTG	M	38	Poorly controlled diabetes and hypertension and proteinuria at baseline. Withdrawn with Grade 1 elevation of creatinine	N	Y
EFV	M	40	Died of fungal sepsis with renal failure part of terminal event	Y	Y
EFV	M	51	Transient increase in creatinine related to ibuprofen	N	N
EFV	F	39	Transient worsening of chronic renal failure attributed to pre-existing cryoglobulinemia	N	Y
EFV	M	33	Episode of acute renal failure resolved	N	N

- One subject on DTG and four subjects on Atripla® had a renal AE.
  - The AE in the DTG subject was judged not to be related to DTG, but the subject was withdrawn from the study.
  - The AE in the subject who died of fungal sepsis in the Atripla® arm was judged to be related to study medication; one other Atripla® subject was withdrawn due to a renal AE, although none of the other AEs were considered related to study drugs.

Curtis LD, et al. IAS 2013. Poster TUPE282

SINGLE: SUMMARY

- DTG + ABC/3TC had statistically superior efficacy vs Atripla®
  - 88% vs 81% reached undetectability through 48 weeks (*P*=0.003)
- DTG was effective regardless of baseline viral load
  - 83% of treatment-naïve patients with HIV-1 RNA >100,000 copies/mL reached undetectability
- No INI or NRTI resistance through 48 weeks with DTG
- DTG + ABC/3TC was better tolerated vs Atripla® with fewer discontinuations
  - 13% vs 27% experienced drug-related AEs (Grades 2 to 4)
  - 2% vs 10% discontinued due to AEs at 48 weeks

Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

ABBREVIATIONS

- 3TC, lamivudine
- ABC, abacavir
- AE, adverse event
- ARF, acute renal failure
- ALT, alanine amino transferase
- AST, aspartate amino transferase
- BID, twice daily
- BL, baseline
- c/mL, copies/mL
- CDC, Centers for Disease Control
- CR, creatinine
- DRV/r, darunavir/ritonavir
- DTG, dolutegravir
- FDA, Food and Drug Administration
- FDC, fixed-dose combination
- FTC, emtricitabine
- HIV, human immunodeficiency virus
- INI, integrase inhibitor
- IQR, inter quartile range
- NRTI, nucleoside reverse transcriptase inhibitor
- PDVF, protocol-defined virologic failure
- QD, once daily
- RAL, raltegravir
- RNA, ribonucleic acid
- TDF, tenofovir
- ULN, upper limit of normal
- URTI, upper respiratory tract infection