HOW DOES A DOLUTEGRAVIR REGIMEN COMPARE TO ATRIPLA® IN TREATMENT-NAÏVE PATIENTS?

SINGLE 96-WEEK DATA

SE/HIV/0009/17I

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

SINGLE[1,2] — 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[3] — 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

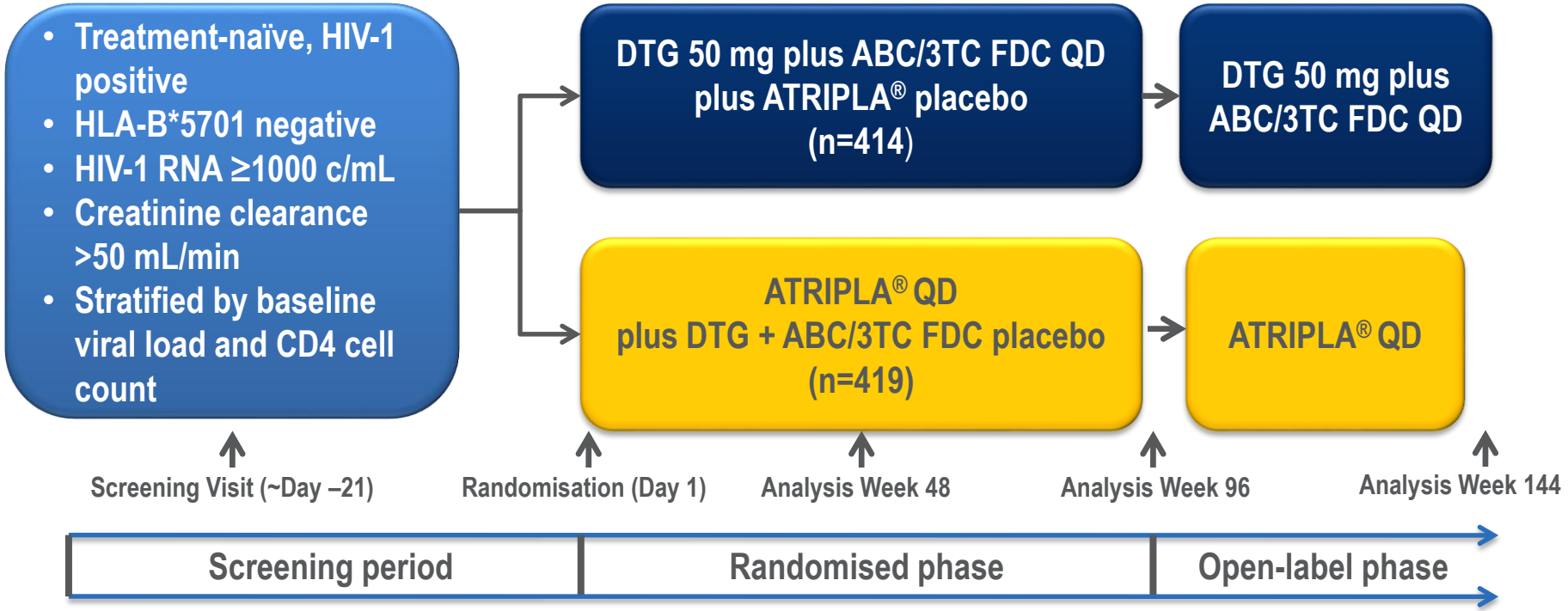
SPRING-2[4,5] — N=822

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. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. Clotet B, et al. *Lancet* 2014; 383: 2222-31
4. Raffi F et al. *Lancet* 2013;381:735–43
5. 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. Poster presented at: 21st CROI; 2014. Poster 543

BASELINE CHARACTERISTICS

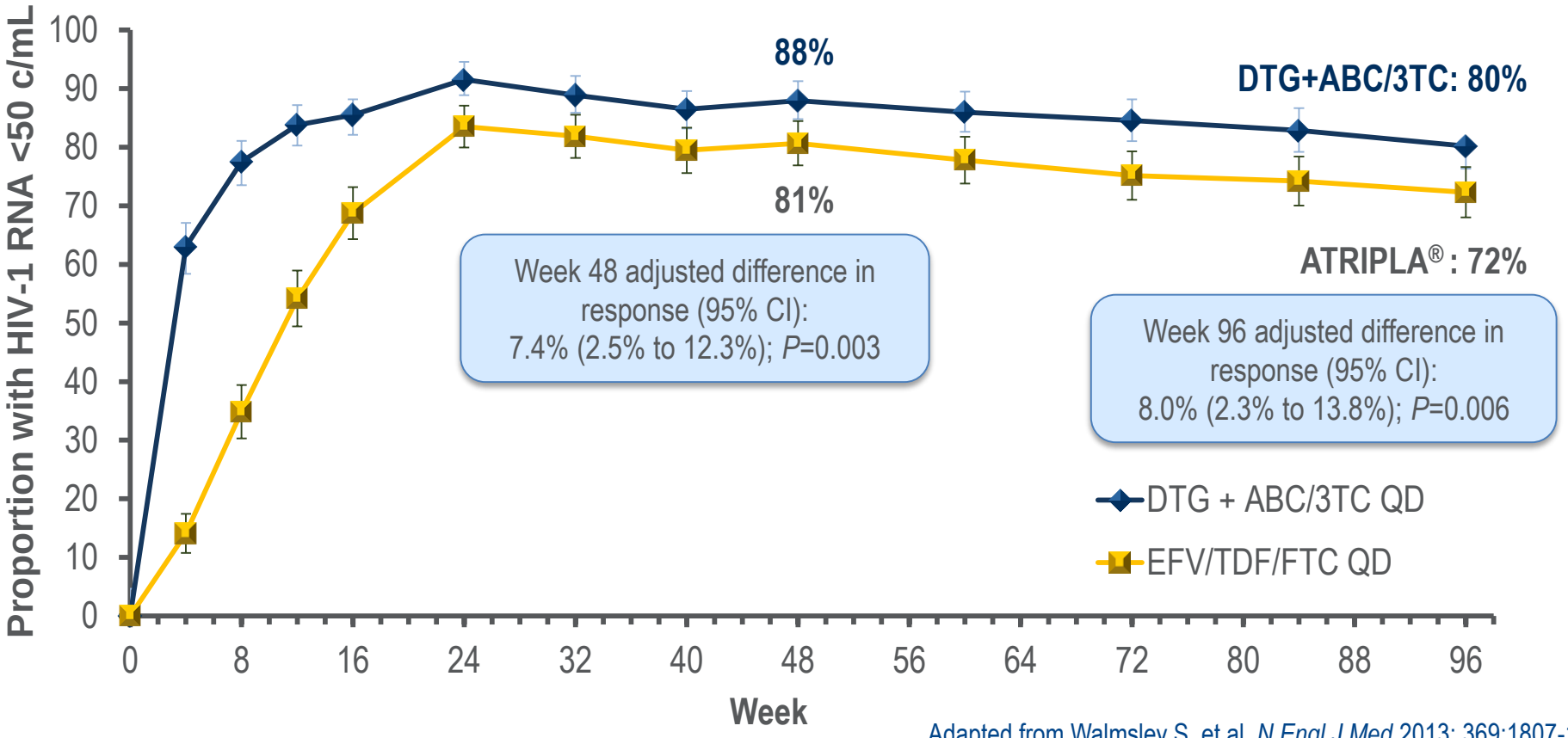
Characteristic	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Median age, years	36	35
Female, %	16	15
African American / African Heritage, %	24	24
CDC class C, %	4	4
Baseline HIV-1 RNA		
Median (log_{10} c/mL)	4.67	4.70
>100,000 c/mL, %	32	31
Median CD4 cell count, cells/mm^3	335	339
<200, %	14	14
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)

DTG + ABC/3TC MAINTAINED STATISTICALLY SUPERIOR EFFICACY VS ATRIPLA® THROUGH TO 96 WEEKS

DTG was statistically superior to Atripla® at Week 48 and Week 96
Subjects receiving DTG achieved faster virologic suppression than Atripla®



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

Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
TIVICAY Produktresumé, 02/2017
Adpated from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

PRIMARY ENDPOINT ANALYSIS: VIROLOGIC RESPONSE OUTCOMES AT WEEK 48

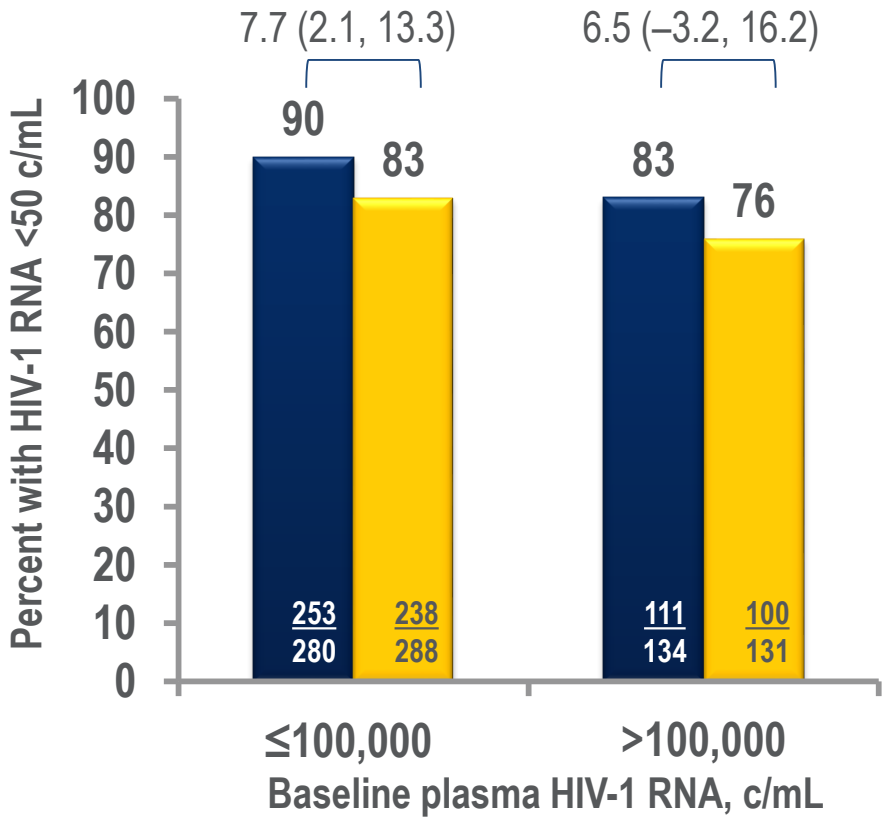
Outcome (Snapshot) at Week 48	DTG 50 mg + ABC/3TC QD (n=414)	ATRIPLA® QD (n=419)
Virologic success, n (%)	364 (88)	338 (81)
Virologic non response, n (%)	21 (5)	26 (6)
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not <50 c/mL	8 (2)	12 (3)
No virologic data at Week 48, n (%)	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, DTG + ABC/3TC was effective regardless of baseline viral load
At 96 weeks, DTG + ABC/3TC was still as effective as Atripla® in patients with high baseline viral loads

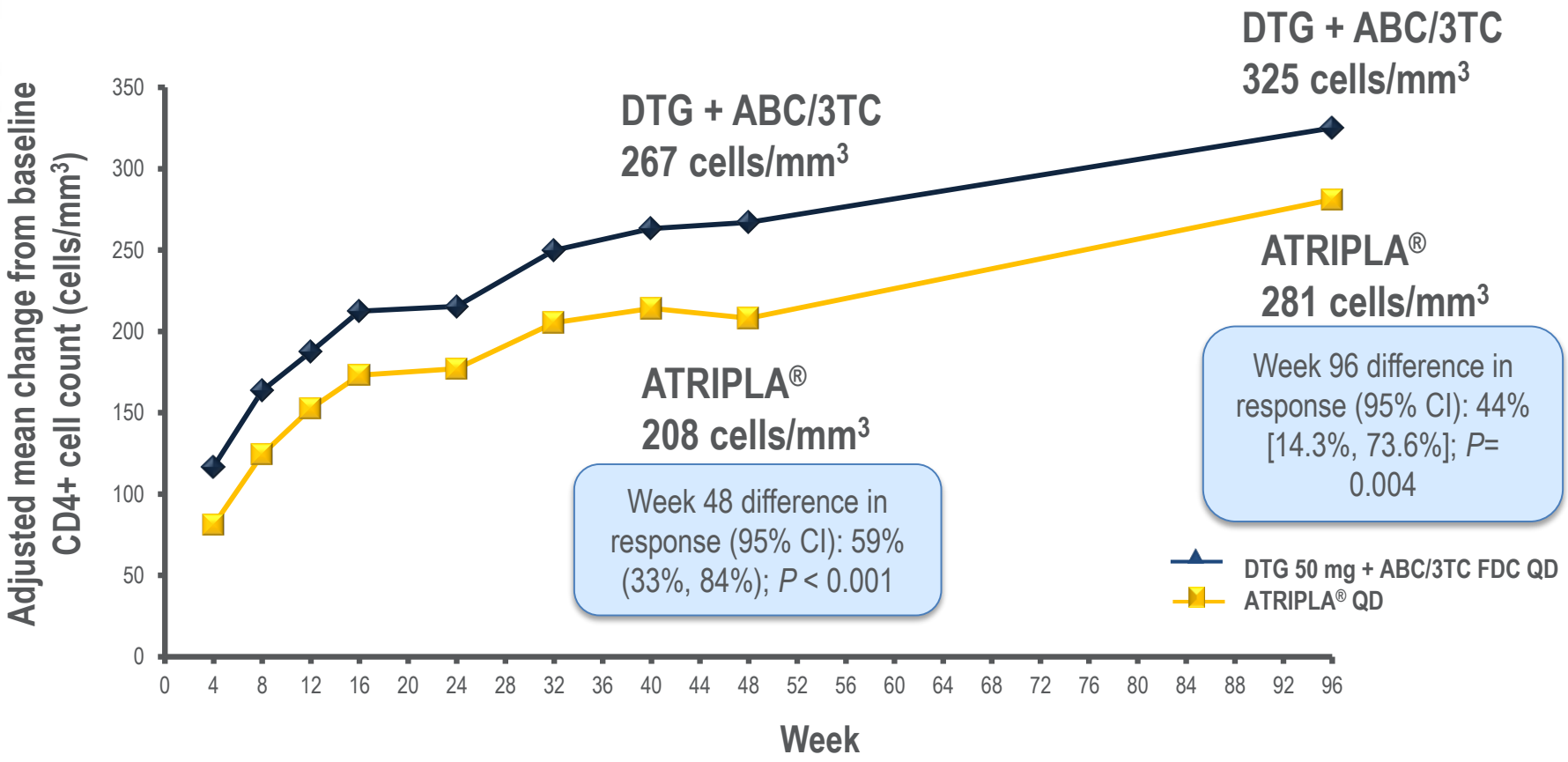


32% of treatment-naïve patients had a baseline viral load >100,000 copies/mL*†

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

TIVICAY Produktresumé, 02/2017
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® THROUGH 48 AND 96 WEEKS



Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
TIVICAY Produktresumé, 02/2017
Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

NO INI OR NRTI RESISTANCE THROUGH 96 WEEKS WITH DTG + ABC/3TC

Amongst DTG-treated subjects, no INI or NRTI mutations were detected at Week 48 or Week 96

	DTG 50 mg +ABC/3TC QD (n=414)		ATRIPLA® QD (n=419)	
	Week 48	Week 96	Week 48	Week 96
Integrase-resistant major substitution	0*	0*	0	N/A
NRTI major mutations	0	0	1†	1†
NNRTI major mutations	N/A	N/A	4‡	6**

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

†Treatment emergent NRTI mutations detected: K65R

‡Treatment-emergent NNRTI mutations detected: K101E (n=1), K103K/N (n=1), G190G/A (n=1) and K103N+G190G/A (n=1)

**Treatment-emergent NNRTI mutations detected: K101E (n=1); K103N (n=1); K103K/N (n=2) , G190A (n=1) ; K103N+G190A (n=1)

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

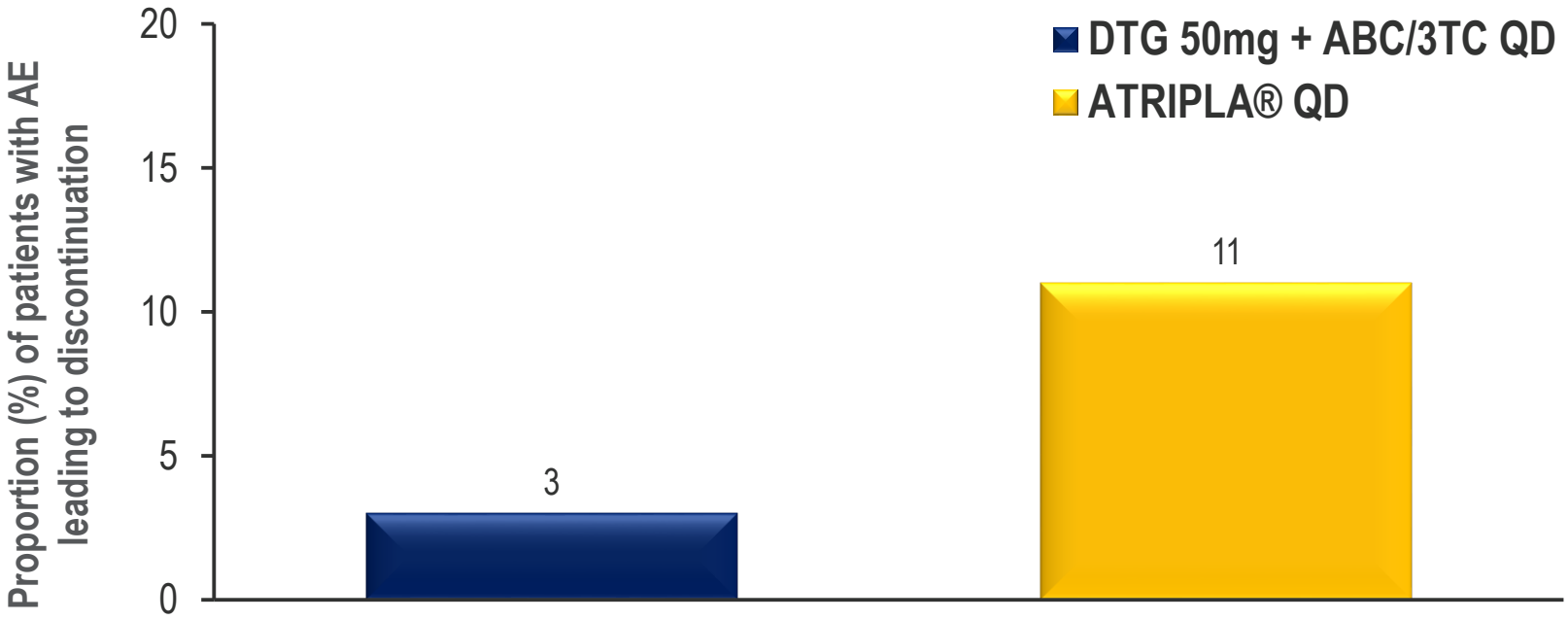
Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (suppl appendix)

TIVICAY Produktresumé, 02/2017

Adpated from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

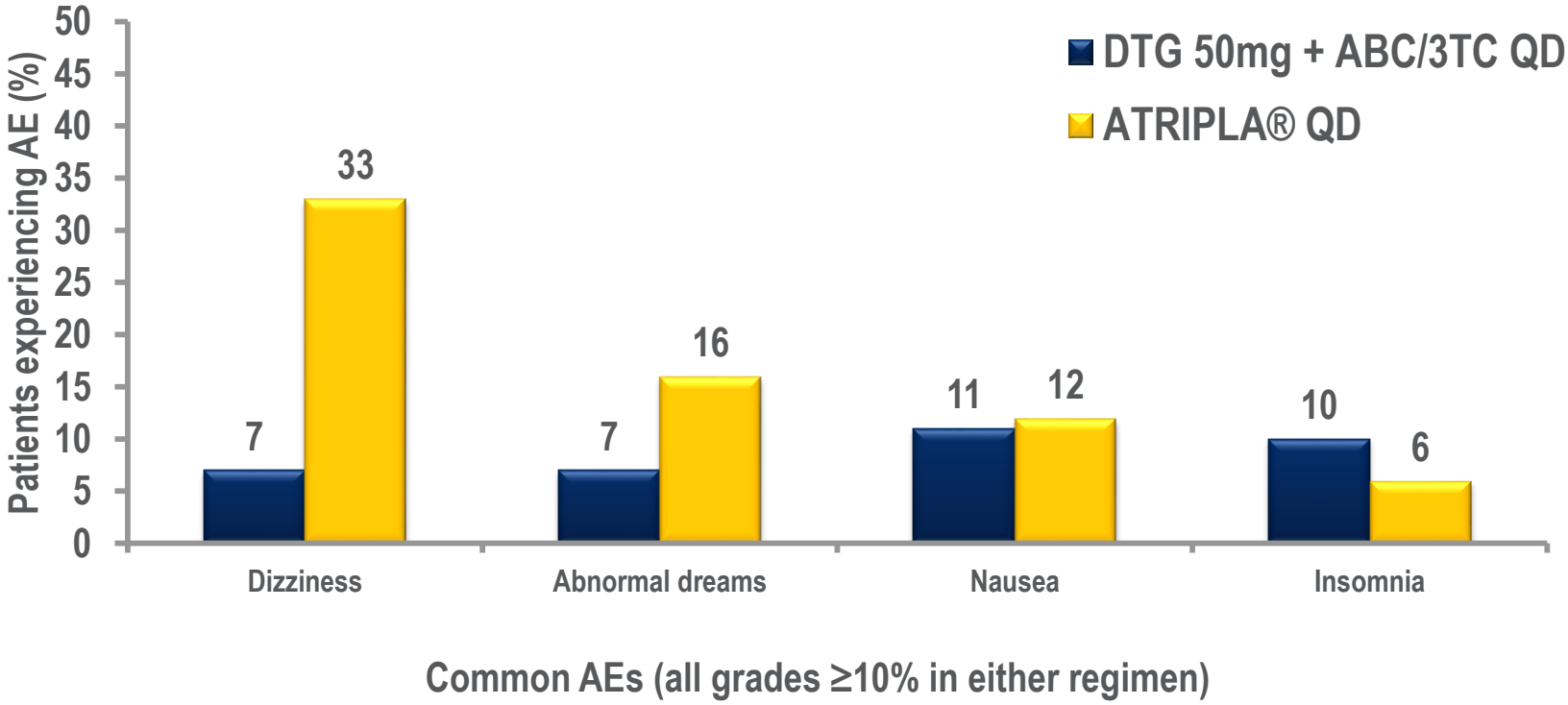
FEWER DISCONTINUATIONS DUE TO ADVERSE EVENTS UP TO 96 WEEKS WITH DTG + ABC/3TC VS ATRIPLA®

Discontinuations due to adverse events were 3% for DTG + ABC/3TC vs 11% for EFV/TDF/FTC at Week 96



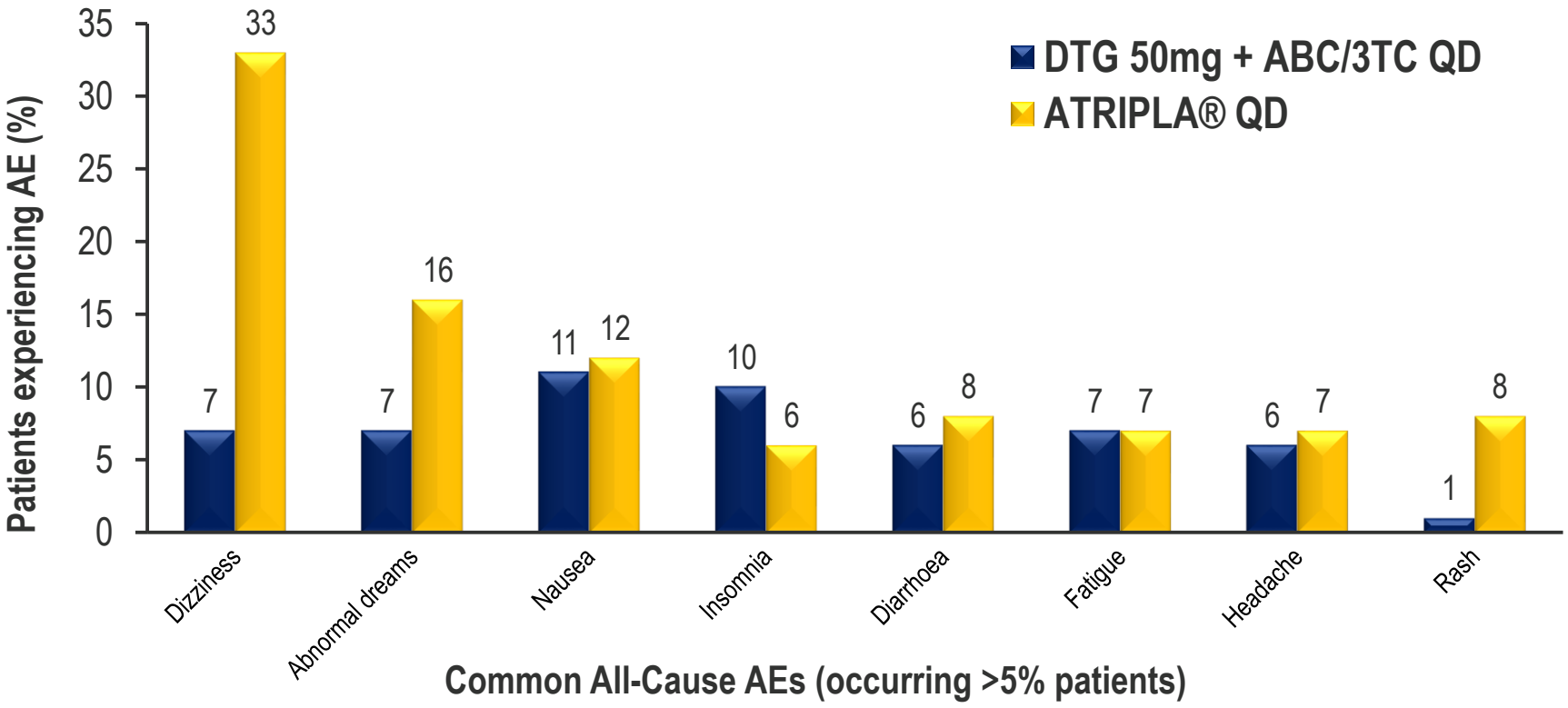
Adpated from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

DTG + ABC/3TC WAS GENERALLY BETTER TOLERATED VS ATRIPLA® AT WEEK 96



Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

DTG + ABC/3TC WAS GENERALLY BETTER TOLERATED VS ATRIPLA® AT WEEK 96



Adapted from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
Data on file. SINGLE 96 week CSR Table 8.8

DTG + ABC/3TC HAD A LOWER IMPACT ON LIVER CHEMISTRY THAN ATRIPLA®

Grade 2 or higher ALT elevations were observed more commonly in the Atripla® arm (24/419; 6%) than in the DTG + ABC/3TC arm (12/414; 3%) at Week 96

Parameter/Criteria, (%) at Week 48	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
Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

THE EFFECT OF DTG + ABC/3TC ON SERUM CREATININE IS NOT CLINICALLY RELEVANT THROUGH TO 96 WEEKS

Small increases in serum creatinine occurred in the first week and remained stable through 96 weeks.

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

	DTG 50 mg+ABC/3TC QD		ATRIPLA® QD	
	Week 48	Week 96	Week 48	Week 96
Urine albumin/creatinine (mg/mmol) Median change (IQR)	0.00 (-0.30, 0.30)	0.00 (-0.30,0.20)	0.05 (-0.20, 0.30)	0.05 (-0.20, 0.30)
Serum creatinine (mg/dL) Median change (IQR)	0.11 (0.05,0.18)	0.14 (0.07,0.20)	-0.01 (-0.06,0.04)	0.02 (-0.04,0.07)

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

TIVICAY Produktresumé, 02/2017

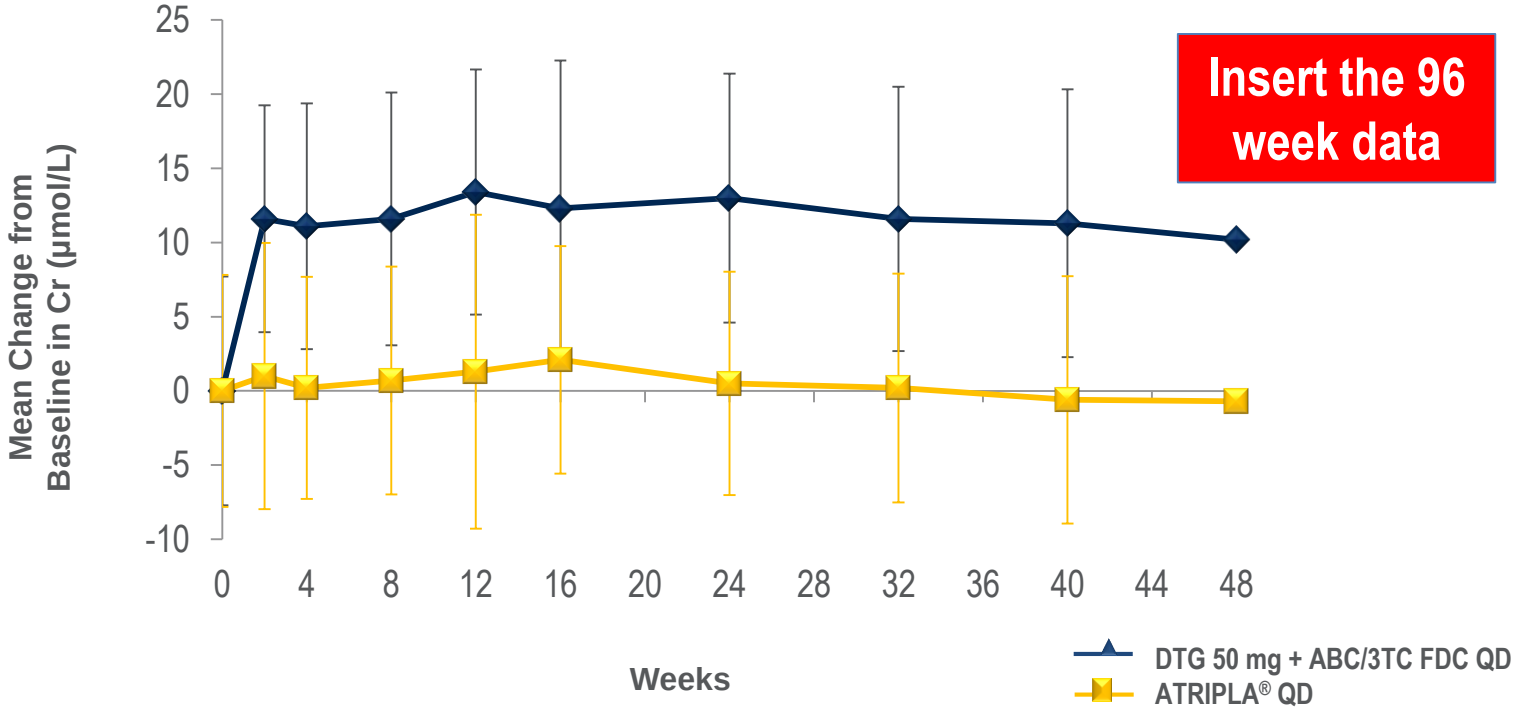
Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996

Adpated from Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

THE EFFECT OF DTG + ABC/3TC ON SERUM CREATININE IS NOT CLINICALLY RELEVANT THROUGH TO 96 WEEKS

Small increases in serum creatinine occurred in the first week and remained stable through 96 weeks.

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



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

TIVICAY Produktresumé, 02/2017

Koteff J et al. *Br J Clin Pharmacol.* 2013;75(4):990-996

Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543

SINGLE: SUMMARY

- DTG + ABC/3TC had statistically superior efficacy vs Atripla®
  - 88% vs 81% reached undetectability at 48 weeks (*P*=0.003)[1]
  - 80% vs 72% reached undetectability at 96 weeks (*P*=0.006)[2,3]
- DTG + ABC/3TC was effective regardless of baseline viral load
  - 83% of treatment-naïve patients with HIV-1 RNA >100,000 copies/mL reached undetectability at 48 weeks[1]
  - DTG + ABC/3TC was still as effective as Atripla® in patients with high baseline viral loads at 96 weeks[2,3]
- DTG + ABC/3TC was generally better tolerated vs Atripla® with fewer discontinuations
  - 3% vs 11% discontinued due to adverse events at 96 weeks[2]
- No INI or NRTI resistance through 96 weeks with DTG regimen[1,2]

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Walmsley S, et al. Poster presented at: 21st CROI 2014. Poster 543
3. TIVICAY Produktresumé, 02/2017

ABBREVIATIONS

- 3TC, lamivudine
- ABC, abacavir
- AE, adverse event
- 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
- HIV, human immunodeficiency virus
- INI, integrase inhibitor
- IQR, inter quartile range
- NRTI, nucleoside reverse transcriptase inhibitor
- QD, once daily
- RAL, raltegravir
- RNA, ribonucleic acid
- ULN, upper limit of normal

MINIMIINFORMATION OCH RAPPORTERING AV BIVERKNINGAR

TIVICAY® (dolutegravir) Rx, EF, ATC kod J05AX12
Detta läkemedel är föremål för utökad övervakning. Filmdragerade tabletter innehållande 10, 25 eller 50 mg dolutegravir (som natrium).
Indikation: TIVICAY är indicerat i kombination med andra antiretrovirala läkemedel för behandling av humant immunbristvirus (hiv) hos vuxna, ungdomar och barn över 6 år.
Kontraindikationer: Överkänslighet mot dolutegravir eller mot något hjälpämne. Samtidig administrering av dofetilid. **Varningar och försiktighet:** Behandling ska förskrivas av läkare med erfarenhet av behandling av hiv-infektion. Dolutegravir är förenat med en risk för överkänslighetsreaktion och bör omedelbart sättas ut vid tecken eller symtom på överkänslighetsreaktion. *Nedsatt njurfunktion:* Ingen dosjustering krävs. *Nedsatt leverfunktion:* Ingen dosjustering krävs för patienter med lätt eller måttlig leverfunktionsnedsättning. Inga data finns för patienter med svår leverfunktionsnedsättning.
Interaktioner: TIVICAY ska administreras två gånger dagligen vid samtidig administrering med efavirenz, nevirapin, tipranavir/ritonavir eller rifampicin. Till patienter med resistens mot integrashämmare ska TIVICAY tas två gånger dagligen och helst tillsammans med mat för att öka exponeringen samtidigt som faktorer som minskar exponeringen för dolutegravir ska undvikas. Detta inkluderar samtidig administrering med magnesium- och aluminiuminnehållande antacida, järn- och kalciumtillskott och multivitaminer. Dolutegravir ökar koncentrationen av metformin. Dosjustering av metformin ska övervägas vid insättning och utsättning av samtidig administrering av dolutegravir och metformin, för att bevara glykemisk kontroll . Metformin elimineras renalt och det är därför viktigt att kontrollera njurfunktionen vid samtidig administrering av dolutegravir. Denna kombination kan öka risken för laktacidos hos patienter med måttligt nedsatt njurfunktion..
Biverkningar: De vanligaste rapporterade biverkningarna som ansågs möjligen eller troligen relaterade till dolutegravir var illamående (13%), diarré (18%) och huvudvärk (13%).
För fullständig förskrivarinformation, se www.fass.se Datum för översyn av produktresumén 02/2017.
TIVICAY är ett registrerat varumärke som tillhör företagsgruppen ViiV Healthcare.

Samtidig administrering av Tivicay och **dofetilid** är kontraindicerad på grund av risken för livshotande toxicitet. Vid tecken på **överkänslighetsreaktion** skall dolutegravir omedelbart utsättas. Kontroller av levervärden rekommenderas hos patienter med **samtidig hepatit B- och/eller C-infektion**. Patienterna ska övervakas vid samtidig behandling med **metformin**.

Om du vill rapportera en biverkning på något av våra läkemedel eller vacciner så kan du kontakta oss på följande sätt:
Rapportera en biverkning via webbformulär
Eller via telefon på 08-638 93 00 (be om att bli kopplad till Biverkningsenheten)