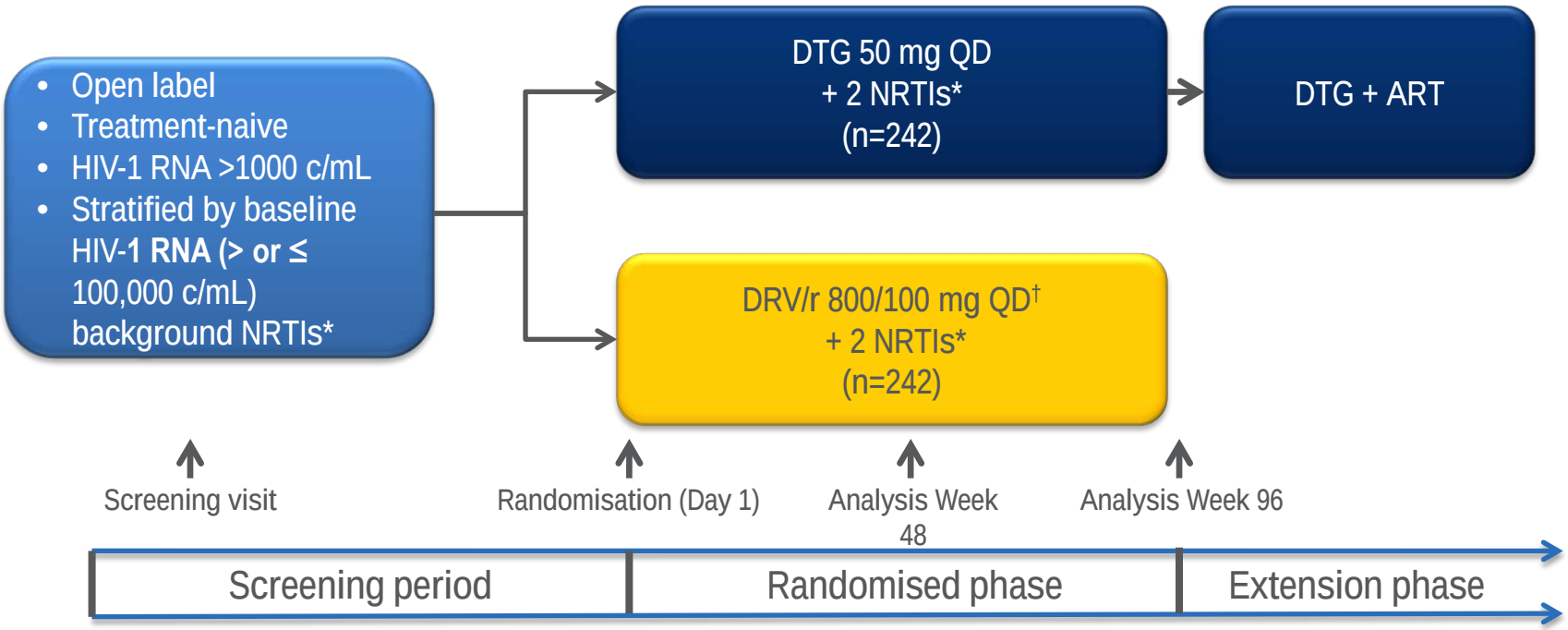
FLAMINGO 96-WEEK PRESENTATION DATA

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

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

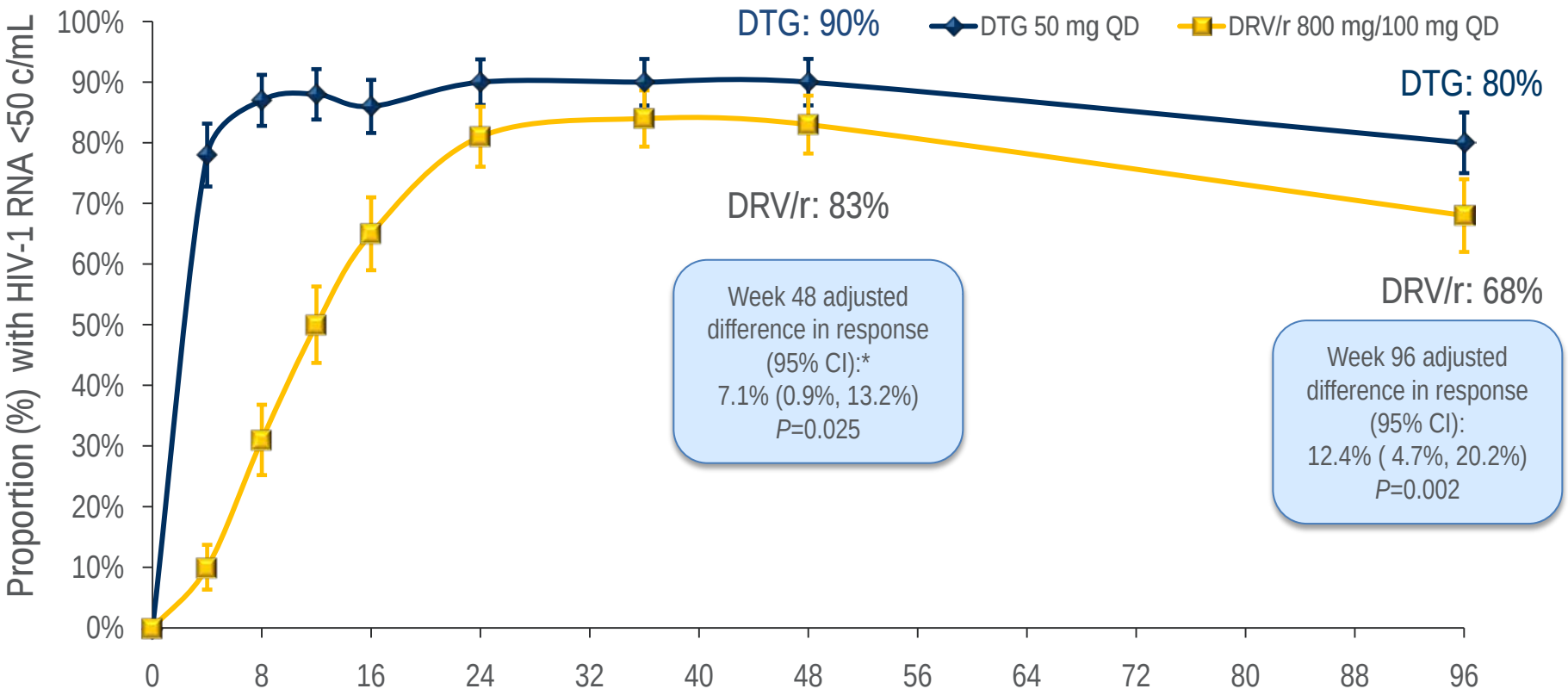
Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	DTG 50 mg QD (n=242)	DRV/r 800/100 mg QD (n=242)
Age, years		
Median (range)	34 (18-67)	34 (19-67)
Gender, n (%)		
Male	211 (87%)	201 (83%)
Female	31 (13%)	41 (17%)
Race, n (%)		
White	173 (71%)	176 (73%)
African American/African heritage	60 (25%)	53 (22%)
Other	8 (3%)	13 (5%)
Baseline plasma HIV-1 RNA		
Median (log_{10} copies/mL)	4.49	4.48
>100,000 copies/mL, n (%)	61 (25%)	61 (25%)
CD4+ T-cell count, cells/mm3 (median)	390	400
HBV/HCV positive, n (%)	9 (4%)/17 (7%)	4 (2%)/15 (6%)
Investigator selected ABC/3TC, n (%)	79 (33%)	80 (33%)

Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31

IN TREATMENT-NAIVE PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS DRV/r UP TO 96 WEEKS

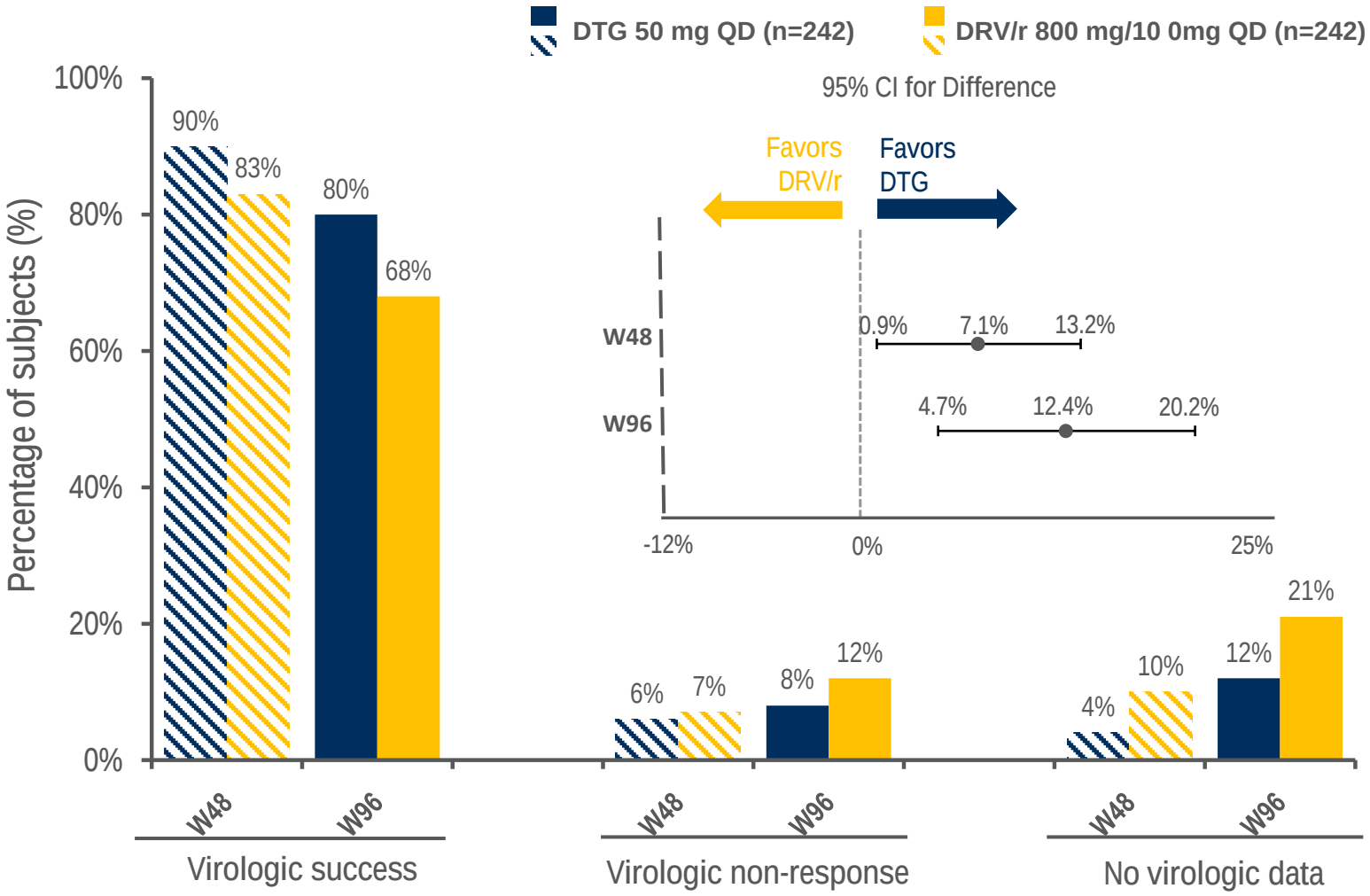


- More rapid virological response with DTG vs DRV/r: 87% vs 31% respectively, at Week 8

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

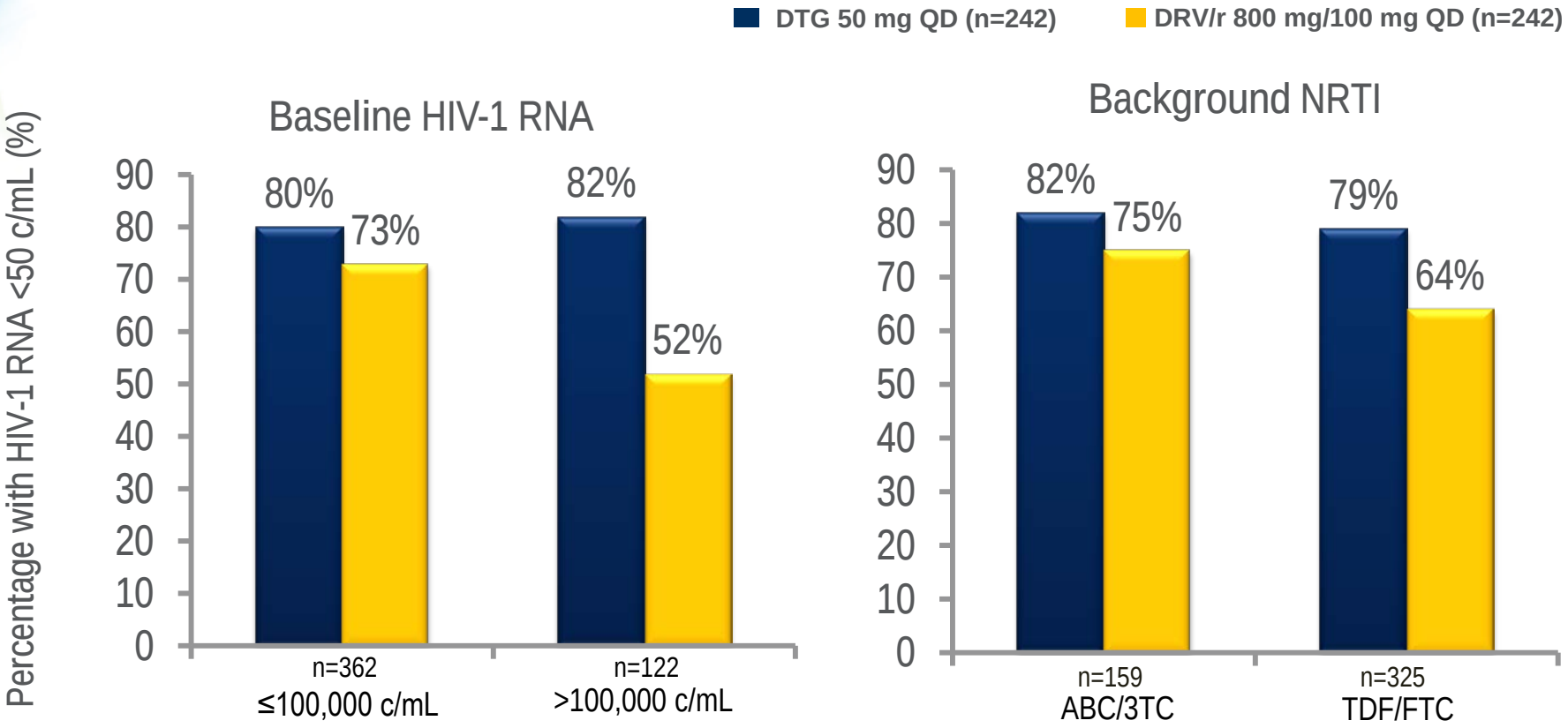
Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31
Adapted from Clotet B, et al. *Lancet* 2014; 383: 2222-31 (Supplementary Appendix)
Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

EFFICACY BY SNAPSHOT: HIV-1 RNA <50 c/mL



Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

DTG WAS EFFECTIVE, REGARDLESS OF BASELINE VIRAL LOAD AND BACKGROUND NRTI, UP TO 96 WEEKS



- DTG outperformed DRV/r in patients with high viral load (>100,000 copies / mL) at weeks 48 and 96

Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

DTG HAD A HIGH BARRIER TO RESISTANCE UP TO 96 WEEKS

No treatment-emergent INI, PI or NRTI resistance was observed up to 96 weeks in either DTG or DRV/r arms

	DTG 50 mg QD	DRV/r 800/100 mg QD
Protocol-defined virologic failure (n%)	2 (<1%)	4 (2%)
INI mutations, n	0	N/A
NRTI mutations, n	0	0
PI mutations, n	N/A	0

- The two subjects with PDVF in the DTG group were at Week 24, whereas in the DRV/r group all four subjects were post-Week 24

PDVF was defined as two consecutive HIV-1 RNA values >200 c/mL, on or after Week 24

Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31
Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

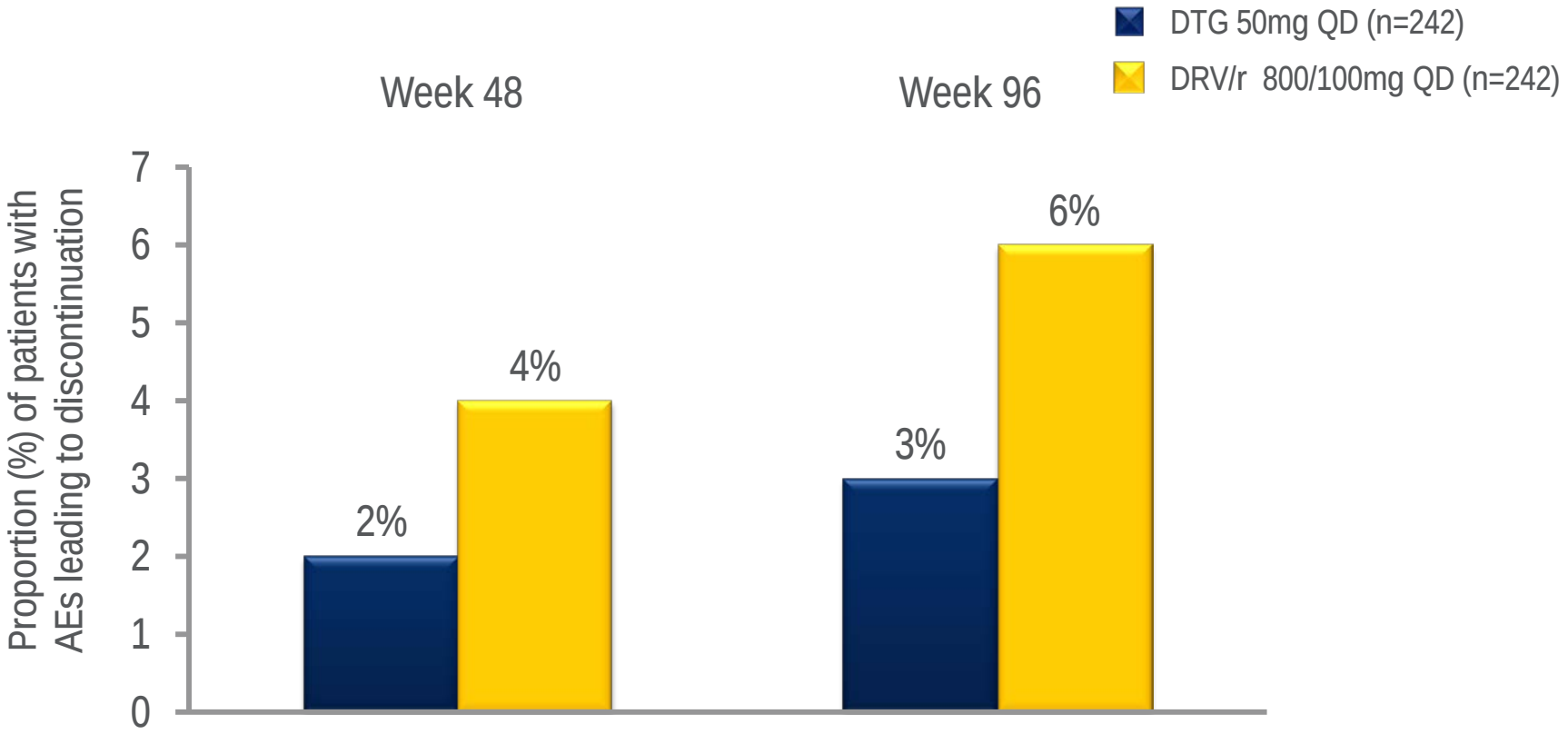
DTG WAS GENERALLY WELL TOLERATED WITH FEW DISCONTINUATIONS UP TO 96 WEEKS

	DTG 50 mg QD (n=242)	DRV/r 800 mg/100 mg QD (n=242)
Overall, n(%)	222 (92%)	217 (90%)
Common AEs (≥ 15% in either arm)		
Diarrhoea	44 (18%)	74 (31%)
Nausea	40 (17%)	48 (20%)
Headache	40 (17%)	26 (11%)
AEs leading to withdrawal	7 (3%)[a]	15 (6%)[b]
Drug-related Grade 3-4	2 (<1%)	4 (2%)
Serious – any event	36 (15%)	21 (9%)
Serious drug-related	3[cd]	0
Fatal AEs	1[e]	0

[*] Post W48 analysis
[a] Suicide, acute hep C, nephroliithiasis*
[b] Hepatitis C, diarrhea/nausea, dysgeusia, renal colic, substance abuse*
[c] DTG + ABC/3TC, suicide attempt with history of suicidality
[d] Includes a, plus n=2 subjects receiving DTG+TDF/FTC (polyarthritis, tendon rupture)
[e] DTG + TDF/FTC, suicide considered unrelated to study drug

Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

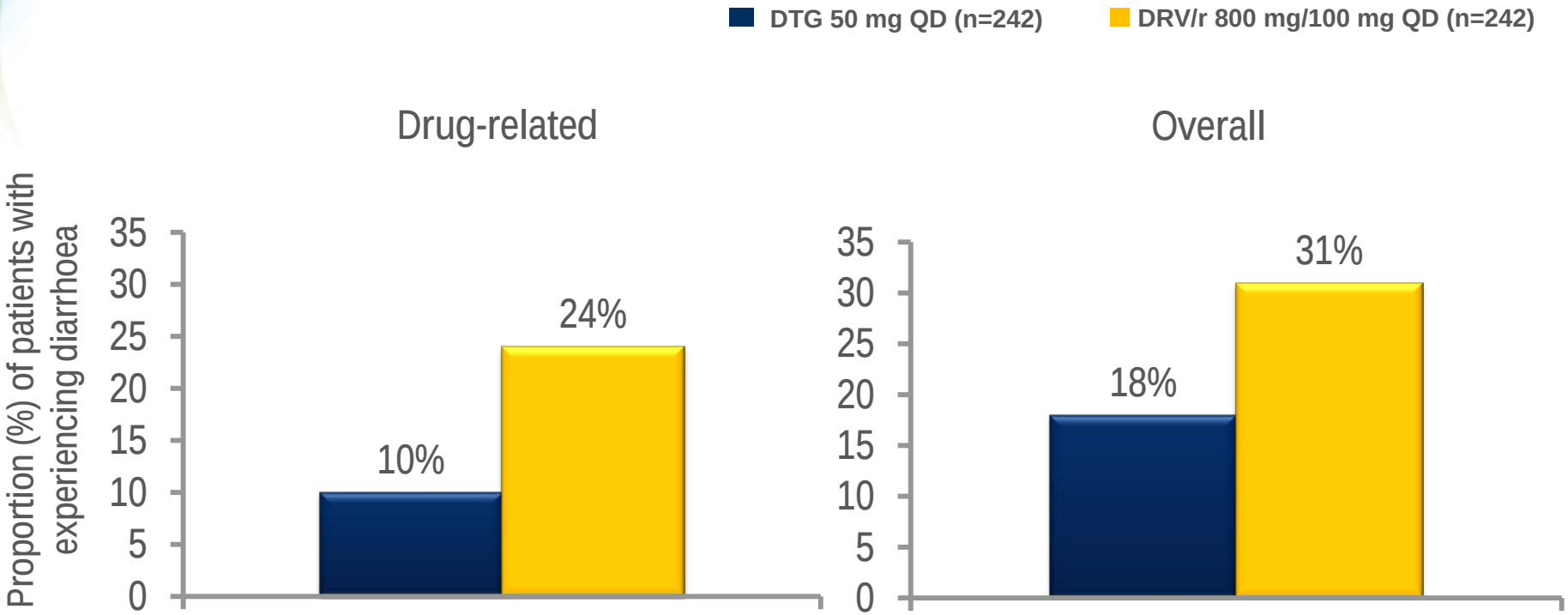
DTG WAS GENERALLY WELL TOLERATED WITH FEW DISCONTINUATIONS UP TO 96 WEEKS



- Discontinuations due to AEs at 96 weeks were 3% for DTG and 6% for DRV/r

Adapted from Clotet B, et al. *Lancet* 2014;383:2222-31
Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

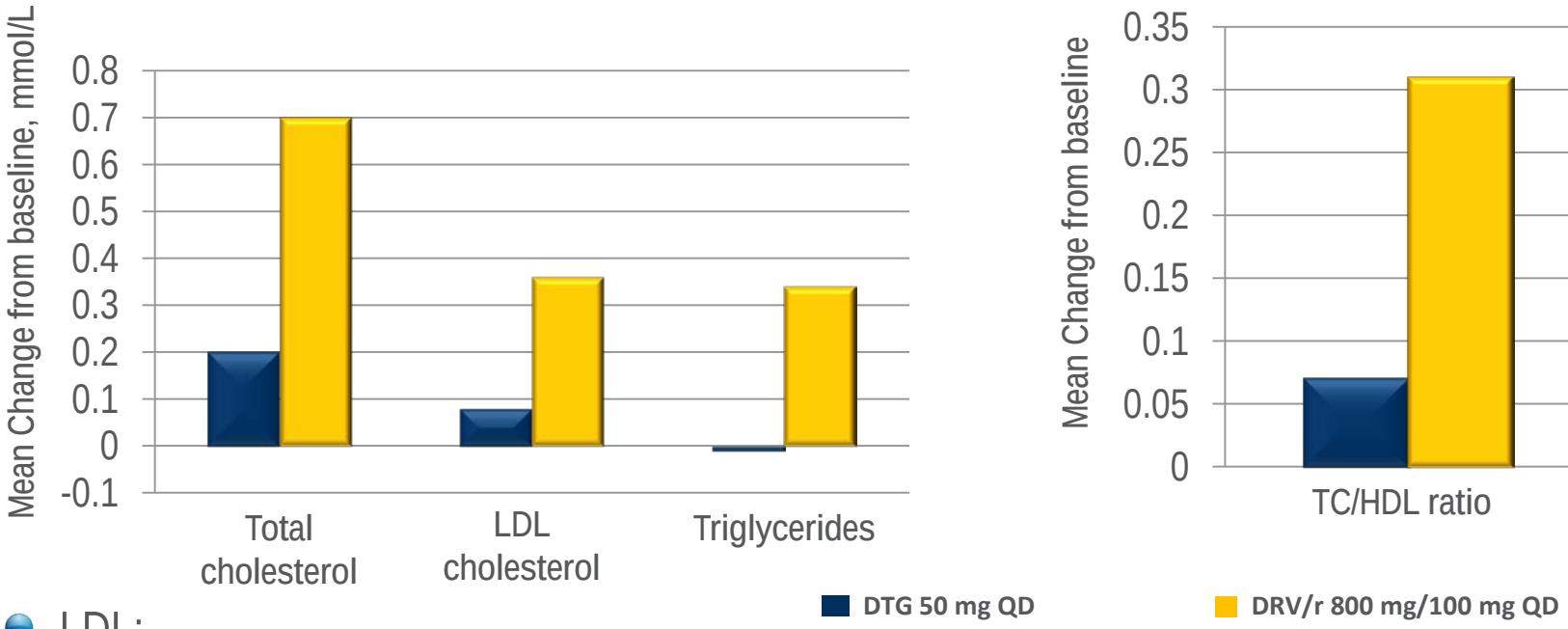
AT 96 WEEKS, DTG WAS GENERALLY WELL TOLERATED WITH LOWER RATES OF DIARRHOEA VS DRV/r



- At 96 weeks, the most common drug-related adverse events in both the DTG and the DRV/r treatment arms were diarrhoea, nausea, and headache

Adapted from Molina J-M, *et al. J Int AIDS Soc.* 2014;17(suppl 3):19490
Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

DTG HAD A FAVOURABLE LDL PROFILE VS DRV/r UP TO 96 WEEKS



- LDL:
  - Higher number of Grade 2 or higher fasting LDL lab abnormalities by Week 96 in the DRV/r arm (22%) vs the DTG arm (7%), *P*<0.001 (pre-specified LOCF analysis).
- CREATININE:
  - At Week 96, the mean change from baseline in serum creatinine was higher in the DTG arm (15.35µmol/L) compared to the DRV/r arm (3.93 µmol/L).

Adapted from Molina JM, et al. Presentation at HIV Drug Therapy Glasgow; Nov 2014

FLAMINGO: SUMMARY

- In treatment-naïve patients, DTG had statistically superior efficacy vs DRV/r
  - 90% vs 83% were undetectable at Week 48 (*P*=0.025)
  - 80% vs 68% remained undetectable at Week 96 (*P*=0.002)
- DTG was effective regardless of baseline viral load
  - At 48 weeks, 93% of treatment-naïve patients with HIV-1 RNA >100,000 copies/mL were undetectable
  - At 96 weeks, 82% of treatment-naïve patients with HIV-1 RNA >100,000 copies/mL remained undetectable
- No treatment-emergent INI, PI or NRTI resistance was seen in either arm up to 96 weeks
- DTG was generally well tolerated up to 96 weeks
  - Drug-related diarrhoea was more common in patients receiving DRV/r vs DTG (24% vs 10%)
  - Significantly fewer patients receiving DTG had ≥Grade 2 fasting LDL values vs DRV/r (7% vs 22%; P<0.001) at 96 weeks
  - Discontinuations due to AEs at 96 weeks were 3% for DTG and 6% for DRV/r

Clotet B, et al. *Lancet* 2014;383:2222-31
Clotet B, et al. *Lancet* 2014;383:2222-31 (Supplementary Appendix)
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Molina J-M, *et al. J Int AIDS Soc.* 2014;17(suppl 3):19490

PRESCRIBING INFORMATION

TIVICAY®▼ (DOLUTEGRAVIR 50MG TABLETS)

(SEE SUMMARY OF PRODUCT CHARACTERISTICS BEFORE PRESCRIBING)

Indication: HIV in >12 years and ≥40kg as part of combination therapy. **Dosing:** 50mg once daily with or without food if no proven/suspected integrase resistance. 50mg twice daily with efavirenz, nevirapine, tipranavir/ritonavir or rifampicin. *Adults with proven/ suspected integrase resistance:* 50mg twice daily preferably with food. *Elderly:* Limited data in 65+ yrs. Caution in severe hepatic impairment. **Contraindications:** Hypersensitivity to any ingredient. Co-administration with dofetilide. **Warnings/precautions:** Risk of hypersensitivity reactions. Discontinue dolutegravir and other suspect agents immediately if suspected. Risks of osteonecrosis, immune reactivation syndrome. Monitor LFTs in Hepatitis B/C co-infection and ensure effective Hepatitis B therapy. Monitor with metformin. Use with etravirine requires boosted PI. Use with Mg/Al-containing antacids, calcium, multivitamins or iron requires dosage separation. Use with St John's Wort and some anti-epileptic drugs not recommended. **Pregnancy/ lactation:** Not recommended. Avoid breast-feeding. **Side effects:** See SPC for full details. Headache, GI disturbance, insomnia, abnormal dreams, dizziness, rash, pruritus, fatigue, elevations of ALT, AST and CPK, hypersensitivity. **Basic NHS costs:** 30 tablets £498.75 EU/1/13/892/001. MA holder: ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Further information available from Customer Contact Centre, GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

POM

Date of approval: November 2014 Zinc code: UK/DLG/0055/13(5)

Adverse events should be reported. For the UK, reporting forms and information can be found at *www.mhra.gov.uk/yellowcard.* Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

Adverse events should be reported. For Ireland, adverse events should be reported directly to the HPRA; Freepost, Pharmacovigilance Section, Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Tel: +353 1 676 4971, *medsafety@hpra.ie.* Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.