VII Curso Avances en Infección VIH y Hepatitis Virales
La Coruña, 1 de Febrero de 2013

Nuevos Fármacos. Nuevas Coformulaciones

Santiago Moreno
Hospital Ramón y Cajal. Madrid.

Tratamiento Antirretroviral Optimo
¿Qué queremos?¿Qué necesitamos?

- Máxima eficacia virológica
  - CV <50 copias/mL en 85% (ITT)
- Excelente tolerancia
  - Suspensiones por EA <5% a 48 semanas
- No toxicidad a largo plazo
  - No lipoatrofia, hiperlipidemia (otros: RCV, hueso, riñón..?)
- No selección de resistencias
  - No resistencias cruzadas. Fácilmente rescatable.
- Comodidad de administración
  - Pocas dosis, pocas pastillas, pocos requerimientos
- Precio

Tratamiento Antirretroviral
¿Qué hemos conseguido?

- El tratamiento antirretroviral actual alcanza cotas elevadas en todos los parámetros medibles
  - Margen de mejora estrecho.
- La simplicidad alcanzada con los regímenes compactos ha contribuido al éxito actual del TAR
  - Debe seguirse en esta línea (regímenes en una sola pastilla)
- Las principales áreas a mejorar incluyen:
  - Tolerabilidad
  - Potenciales efectos a largo plazo
  - Mayores efectos sobre aspectos inmunológicos e inflamatorios

Nuevos Fármacos.
Nuevas Coformulaciones.

- Análogos de Nucleósidos
  - Profármaco de Tenofovir
- No Análogos de Nucleósidos
  - Rilpivirina
- Inhibidores de la Integrasa
  - Elvitegravir
  - Dolutegravir

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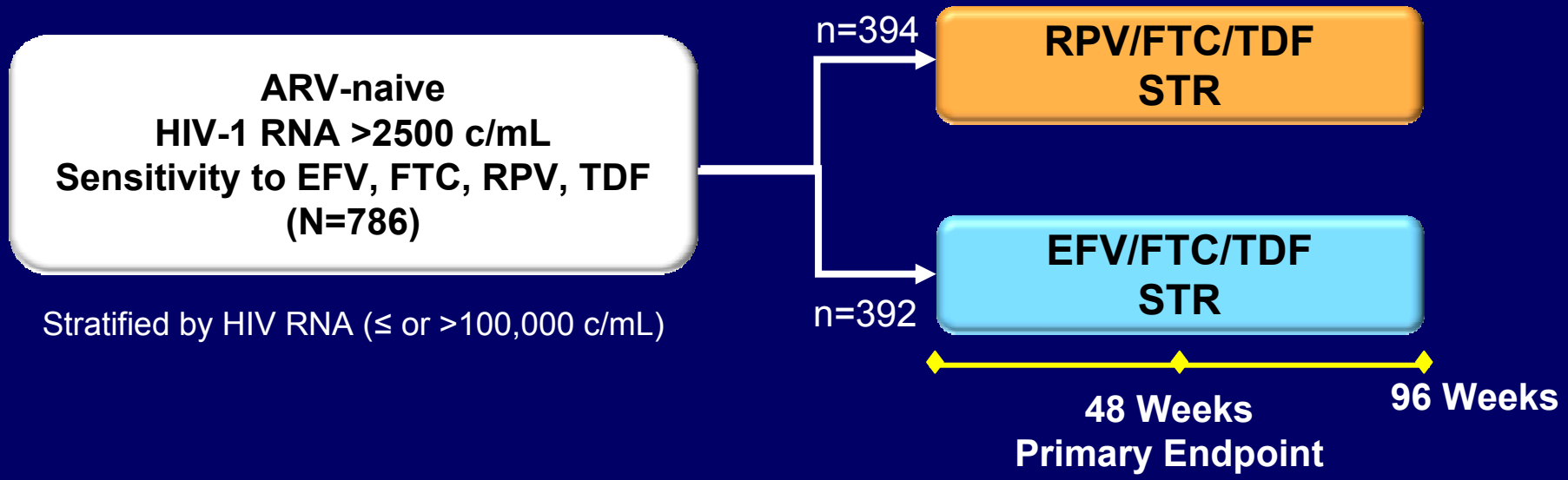
STaR
Study Design

Multicenter, international, randomized, open-label, Phase 3b, 96-week study



Primary endpoint: Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot analysis); non-inferiority margin of 12%

Secondary endpoints: Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (FDA Snapshot analysis)
Change in CD4 cell count at Weeks 48 and 96
Genotype/phenotype resistance at time of virologic failure

STaR

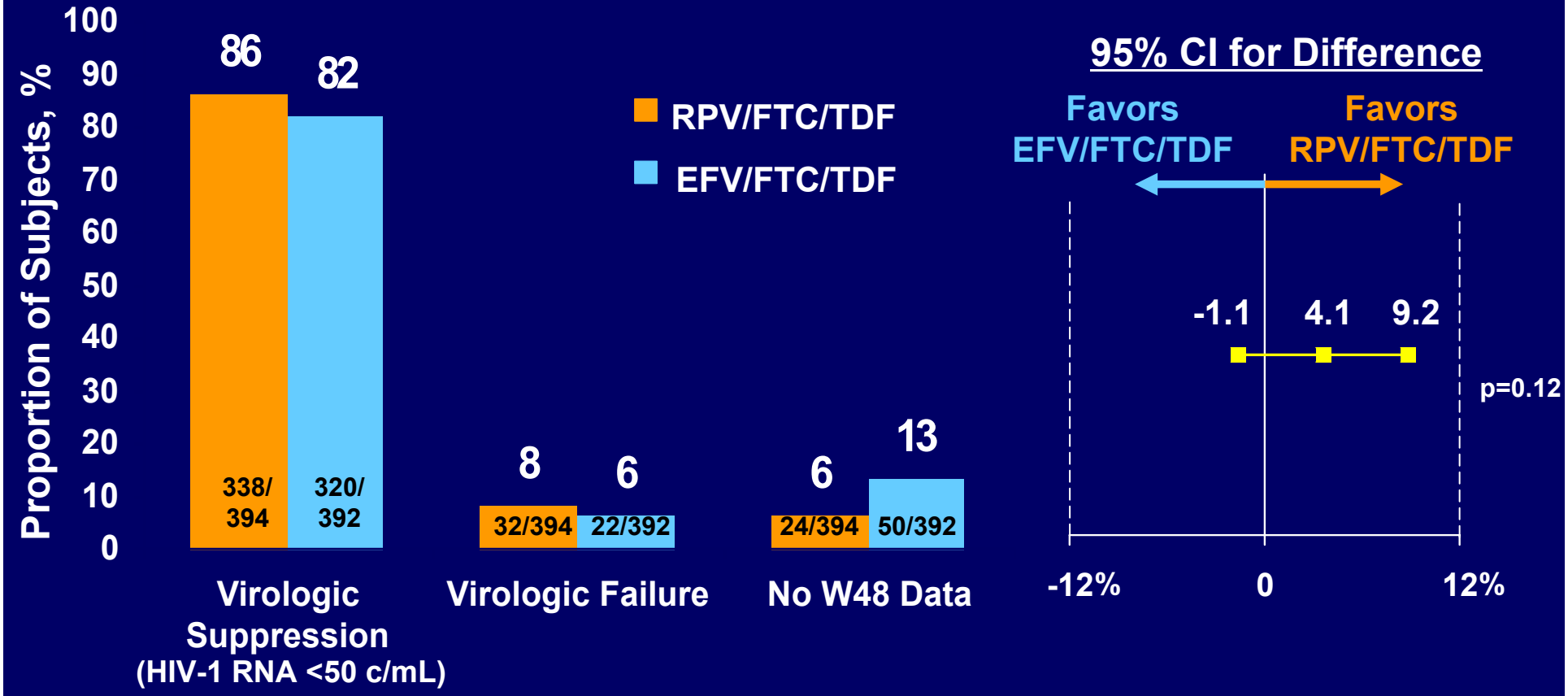
Baseline Demographics and Characteristics

	RPV/FTC/TDF	EFV/FTC/TDF
Median age, years (IQR)	37 (29, 45)	35 (28, 45)
Male	93%	93%
White race	68%	67%
Black race	25%	24%
Latino ethnicity	15%	19%
Mean CD4 cell count, cells/mm^3 (SD)	396 (180)	385 (187)
HIV-1 RNA, log10 c/mL, mean (SD)	4.8 (0.7)	4.8 (0.6)
≤100,000 c/mL, n (%)	260 (66%)	250 (64%)
>100,000 to ≤500,000 c/mL, n (%)	98 (25%)	117 (30%)
>500,000 c/mL, n (%)	36 (9%)	25 (6%)

Research sites include Australia, Austria, Belgium, Canada, France, Germany, Italy, Portugal, Spain, Switzerland, United Kingdom, United States and Puerto Rico

STaR
Virologic Suppression and CD4 Change at Week 48
FDA Snapshot Analysis – ITT Population

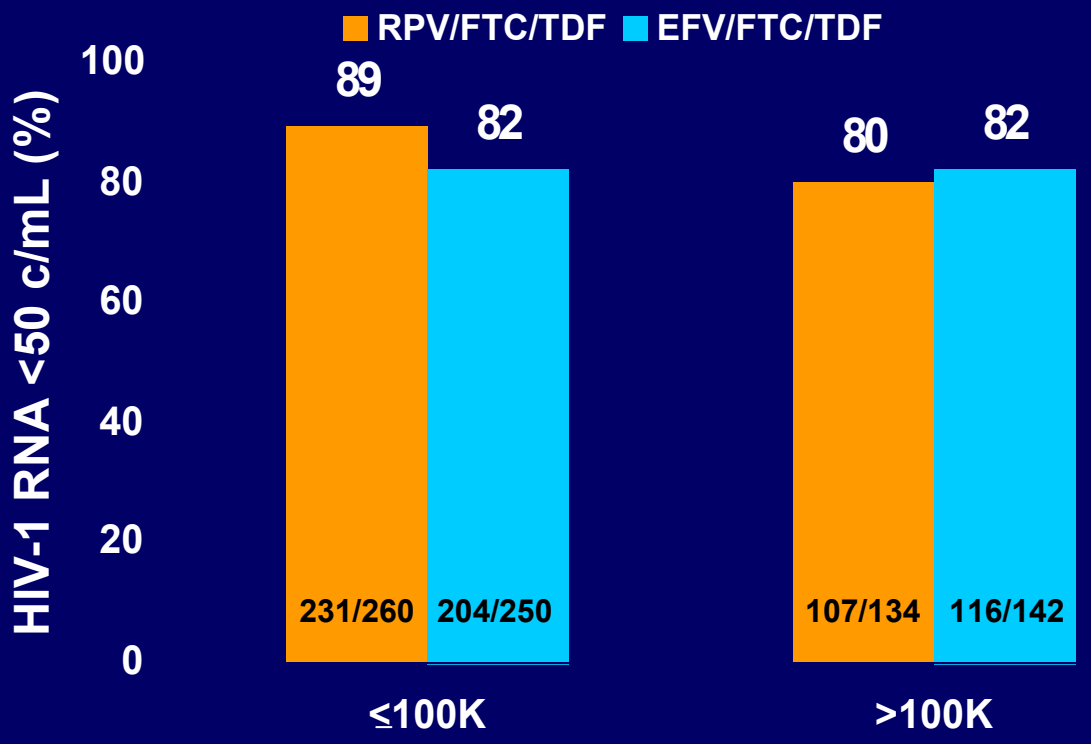
RPVFTC//TDF is non-inferior to EFV/FTC/TDF

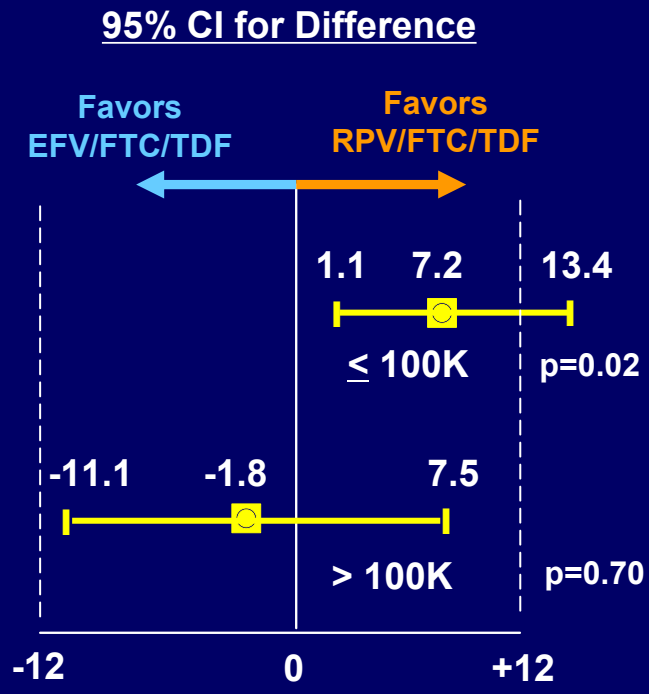


CD4 count change (cells/mm^3): RPV/FTC/TDF +200 vs EFV/FTC/TDF +191 (p=0.34)

STaR

Virologic Suppression at Week 48 FDA Snapshot Analysis by Baseline HIV-1 RNA Stratified by 100,000 c/mL

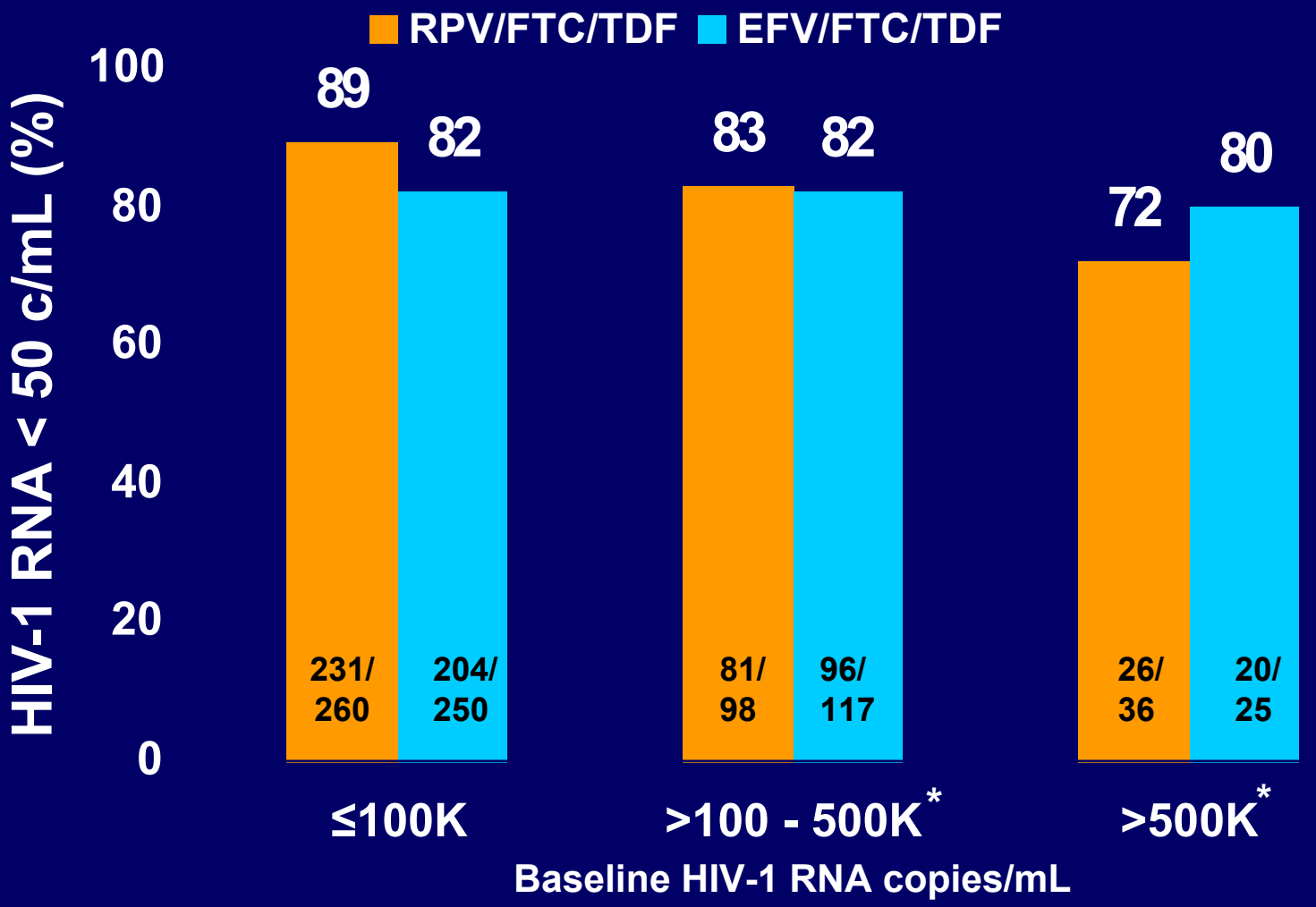




RPV/FTC/TDF compared to EFV/FTC/TDF
Superior for subjects with baseline HIV-1 RNA ≤100,000 c/mL
Non-inferior for subjects with baseline HIV-1 RNA >100,000 c/mL

STaR

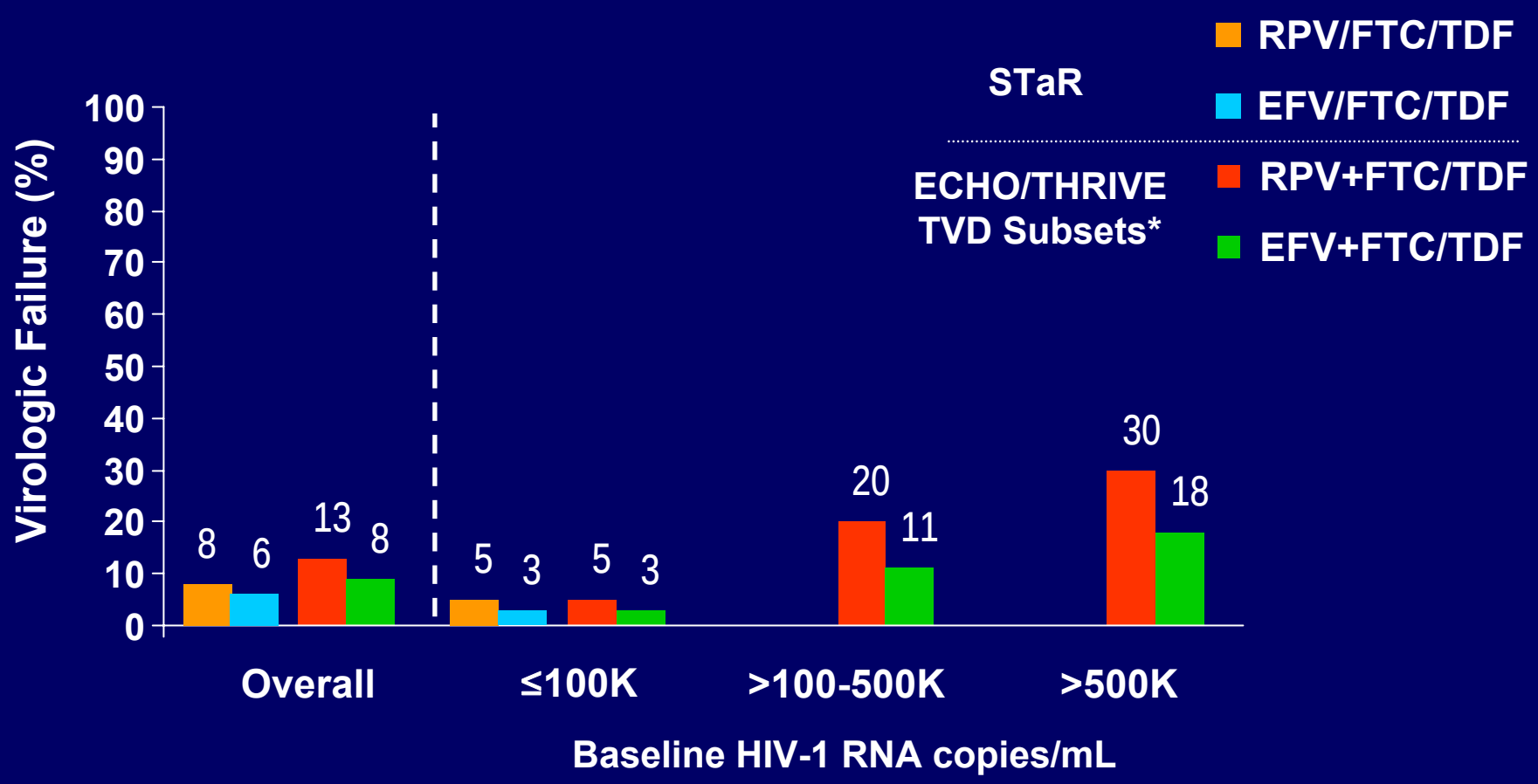
Virologic Suppression at Week 48 FDA Snapshot Analysis by Baseline HIV-1 RNA



* Post hoc analyses; analyses for non-inferiority only pre-specified for ≤100,000 c/mL and >100,000 c/mL

STaR & ECHO/THRIVE

Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA

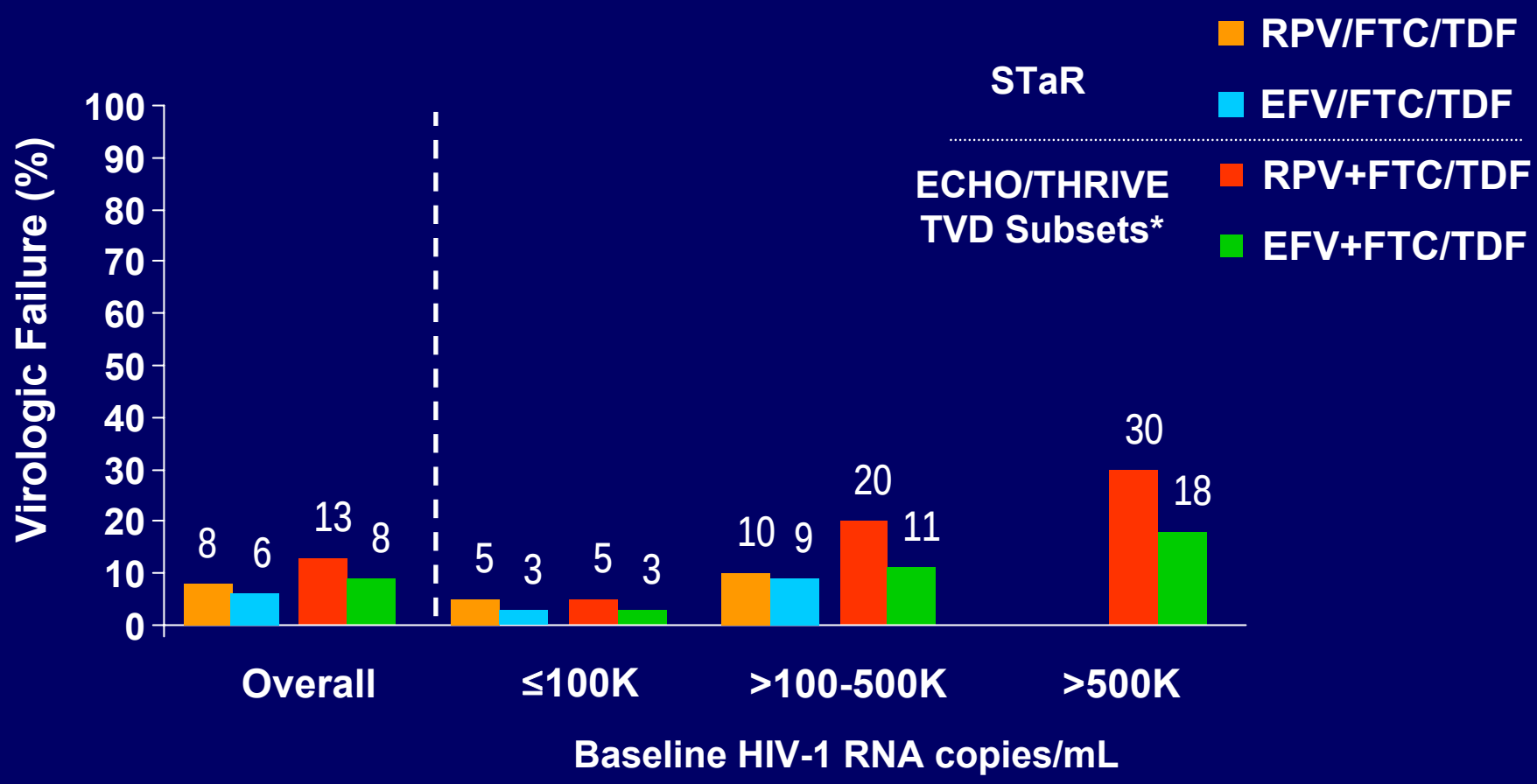


ECHO/THRIVE: Two Phase III double-blinded, double dummy, mulitcenter 96 week studies in treatment-naïve HIV-1 infected subjects randomized to receive either RPV (25mg) or EFV (600mg) in combination with 2 NRTIs (ECHO, FTC/TDF; THRIVE, Investigator's choice [FTC/TDF, n=406; 3TC/AZT, n=204; 3TC/ABC, n=68]). In the pooled TVD subset analysis (N=1096), RPV+TVD was non-inferior to EFV+TVD (HIV-1 RNA <50 c/mL [83%, 81%])

*COMPLERA Prescribing Information. Gilead Sciences Inc. 2011.

STaR & ECHO/THRIVE

Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA



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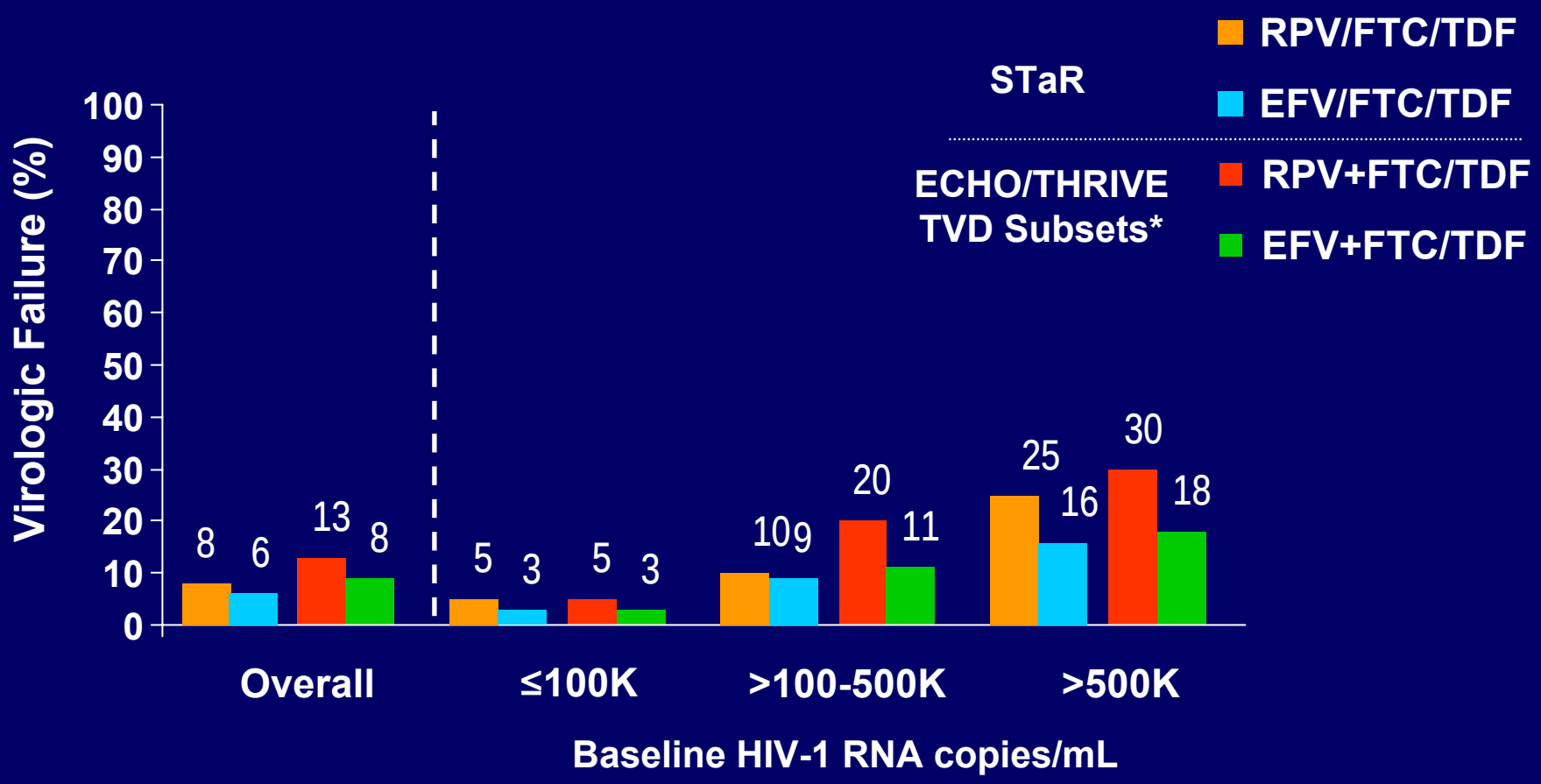
STaR & ECHO/THRIVE

Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA



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STaR vs ECHO and THRIVE

Resistance Analysis Through Week 48

	STaR*		ECHO/THRIVE TVD Subset†	
	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	RPV+FTC/TDF (n=550)	EFV+FTC/TDF (n=546)
Subjects with Resistance Data			11%	3%
Subjects with Resistance to ARVs			7%	2%
Any Primary NNRTI-R			6%	2%
Key NNRTI-R			E138K/Q (4%)	K103N (1%)
			Y181C/I (1%)	
			K101E (1%)	
Any Primary NRTI-R			7%	1%
Key NRTI-R			M184V/I(6%)	M184V/I (1%)
			K65R/N (1%)	K65R/N (0.4%)
Within Baseline (BL) HIV-1 RNA				
≤100,000 copies/mL at BL			2%	1%
>100,000–500,000 copies/mL at BL			9%	2%
>500,000 copies/mL at BL			21%	7%

*Subjects who experienced suboptimal virologic response (HIV-1 RNA ≥50 c/mL and <1 log10 below BL at W8 and confirmed at subsequent visit), virologic rebound (2 consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50 c/mL, or >1 log10 increase from nadir), or had HIV-1 RNA ≥400 c/mL at W48 or their last visit (at or after W8)
‡ Subjects who were either never suppressed (never having achieved 2 consecutive VL values <50 c/mL and having an increase in HIV-1 RNA ≥0.5 log10 c/mL above the nadir) or virologic rebound (first achieving two consecutive HIV-1 RNA values <50 c/mL and having 2 consecutive, or single when last available, HIV-1 RNA values ≥50 c/mL). Rimsky et al (2012) JAIDS

STaR vs ECHO and THRIVE

Resistance Analysis Through Week 48

	STaR*		ECHO/THRIVE TVD Subset†	
	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	RPV+FTC/TDF (n=550)	EFV+FTC/TDF (n=546)
Subjects with Resistance Data	5%	2%	11%	3%
Subjects with Resistance to ARVs	4%	1%	7%	2%
Any Primary NNRTI-R	4%	1%	6%	2%
Key NNRTI-R	E138K/Q (2%)	K103N (0.3%)	E138K/Q (4%)	K103N (1%)
	Y181C/I (2%)		Y181C/I (1%)	
	K101E (1%)		K101E (1%)	
Any Primary NRTI-R	4%	0.3%	7%	1%
Key NRTI-R	M184V/I (4%)	M184I (0.3%)	M184V/I(6%)	M184V/I (1%)
	K65R/N (1%)		K65R/N (1%)	K65R/N (0.4%)
Within Baseline (BL) HIV-1 RNA				
≤100,000 copies/mL at BL	2%	1%	2%	1%
>100,000–500,000 copies/mL at BL	5%	0	9%	2%
>500,000 copies/mL at BL	19%	4%	21%	7%

The STRs used in STaR, compared to the STR components used in ECHO and THRIVE, demonstrated less emergent resistance

*Subjects who experienced suboptimal virologic response (HIV-1 RNA ≥50 c/mL and <1 log10 below BL at W8 and confirmed at subsequent visit), virologic rebound (2 consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50 c/mL, or >1 log10 increase from nadir), or had HIV-1 RNA ≥400 c/mL at W48 or their last visit (at or after W8)

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STaR

All Grades Treatment-Emergent Pre-specified Adverse Events* Through Week 48

	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	
Nervous System Events, n (%)	**117 (30%)**	**198 (51%)**	**p< 0.001**
Events >5% of subjects, either arm			
Dizziness, vertigo, balance disorder	30 (8%)	100 (26%)	
Insomnia	38 (10%)	55 (14%)	
Somnolence	10 (3%)	27 (7%)	
Headache	49 (12%)	53 (14%)	
Psychiatric Events, n (%)	**62 (16%)**	**147 (38%)**	**p< 0.001**
Events >5% of subjects†, either arm			
Abnormal Dreams	23 (6%)	96 (25%)	
Depression	26 (7%)	35 (9%)	
Anxiety, nervousness	20 (5%)	34 (9%)	

*prespecified evaluation for common adverse events, US Efavirenz Prescribing Information

† 1 (0.3%) suicide occurred in the EFV/FTC/TDF arm, day 36 of study

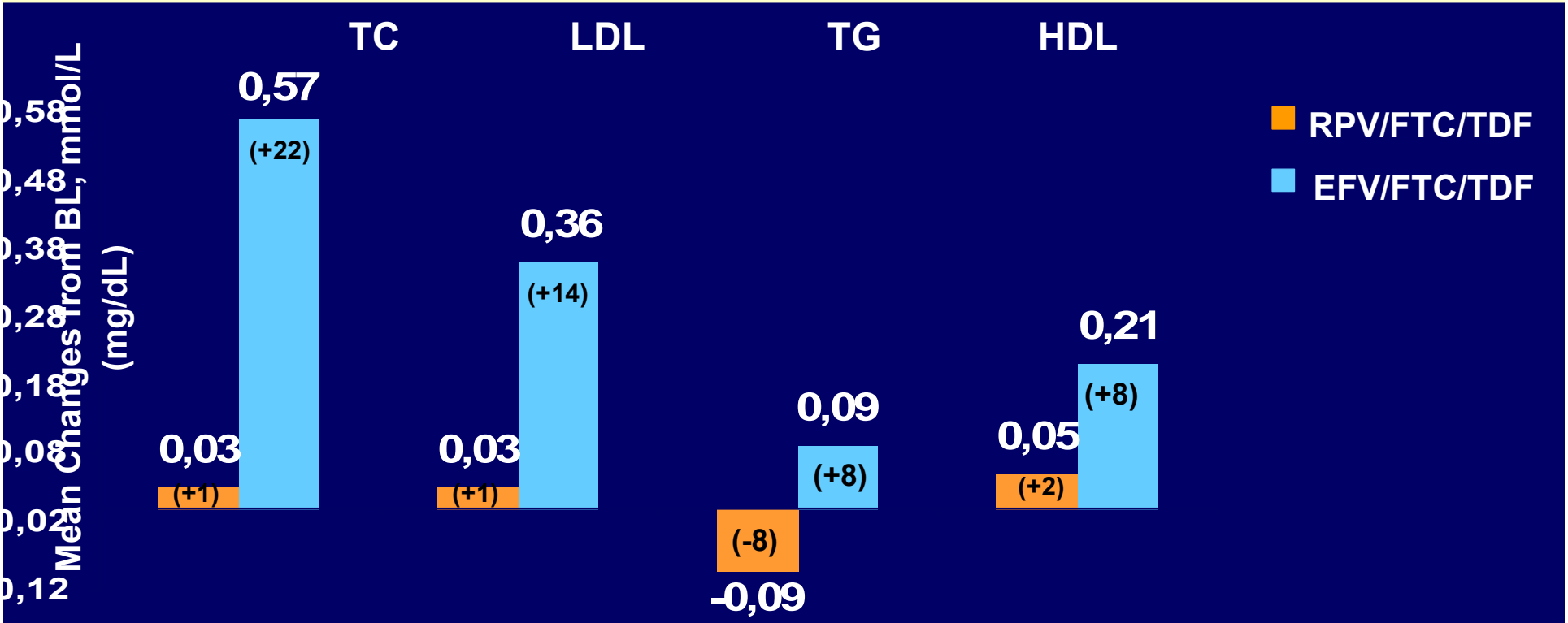
STaR

Adverse Events Leading to Discontinuation of Study Drug Through Week 48

	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	
Discontinuations* Due to Adverse Event (AE), n (%)	**10 (2.5%)**	**34 (8.7%)**	**P<0.001**
AE leading to discontinuation in >1 subject in either arm			
Nervous System Events			
Dizziness	**0**	**5 (1.3%)**	
Abnormal Dreams or Nightmare	**0**	**6 (1.5%)**	
Insomnia	**1 (0.3%)**	**3 (0.8%)**	
Psychiatric Disorders			
Depression, Anxiety or Depressed Mood	**0**	**9 (2.3%)**	
Suicidal Ideation	**0**	**2 (0.5%)**	
GI, General, Skin Disorders			
Diarrhea	**0**	**2 (0.5%)**	
Fatigue	**0**	**2 (0.5%)**	
Pyrexia	**0**	**2 (0.5%)**	
Toxic Skin Eruption	**0**	**2 (0.5%)**	

*per safety population

STaR
Changes from Baseline Through Week 48 in Fasting Lipids



p<0.001 for all the above comparisons between treatment groups using ANOVA

Mean Baseline Values, mmol/L	4.24	4.22	2.69	2.66	1.37	1.46	1.14	1.14

Change in TC:HDL at Week 48 was -0.2 in both arms

TC - total cholesterol, LDL - low-density lipoprotein, TG - triglycerides, HDL - high-density lipoprotein

STaR
Conclusions

- **Overall, RPV/TDF/FTC was non-inferior to EFV/FTC/TDF through Week 48 for the primary endpoint of virologic suppression**
  - **Superior** when baseline HIV-1 RNA ≤100,000 copies/mL
  - **Non-inferior** when baseline HIV-1 RNA >100,000 copies/mL
- **Similar overall virologic failure rates for RPV/FTC/TDF (8%) vs EFV/FTC/TDF (6%) occurred through Week 48**
  - Virologic failure rates by baseline HIV-1 RNA
    - ≤100,000 c/mL: 5% vs 3%
    - >100,000-500,000 c/mL: 10% vs 9%
    - >500,000 c/mL: 25% vs 16%
- **RPV/FTC/TDF is significantly better tolerated than EFV/FTC/TDF**
    - Fewer nervous system and psychiatric adverse events
    - Fewer discontinuations due to adverse events

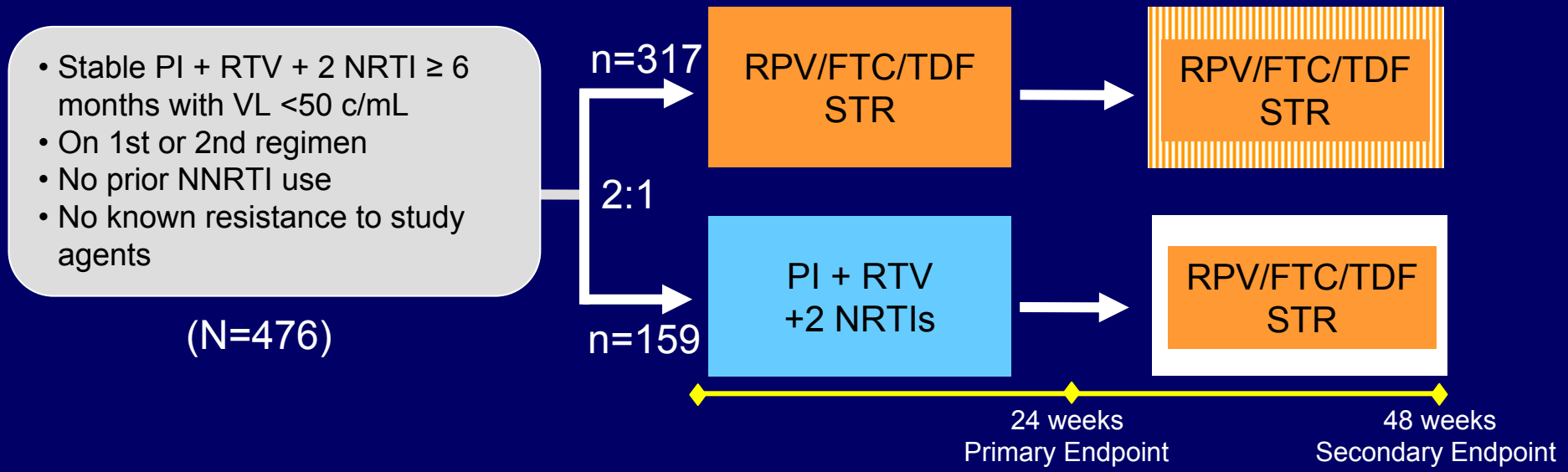
SPIRIT: Switching to Emtricitibine/Rilpivirine/Tenofovir DF Single-Tablet Regimen from Boosted Protease Inhibitor Maintains HIV Suppression through Week 48

Martin Fisher, Frank Pallela, Pablo Tebas, Brian Gazzard, Peter Ruane, Jan van Lunzen, David Shamblaw, Jason Flamm, Ramin Ebrahimi, Kirsten White, Bill Guyer, Danielle Porter, Todd Fralich

Eleventh International Congress on Drug Therapy in HIV Infection
Glasgow, Scotland
November 14, 2012
GS-US-264-0106 NCT01252940
Poster P285

SPIRIT
Study Design

Switching boosted PI to Rilpivirine In-combination with Truvada as an STR
Multicenter, international, randomized, open-label, Phase 3b, 48-week study



Primary Endpoint:

Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks[1]

Secondary Endpoints:

Proportion of subjects on RPV/FTC/TDF who have HIV1 RNA <50 copies/mL at Week 48
Change in fasting lipid parameters and CD4 cell count at 24[1,2] and 48 weeks
Safety and tolerability to PI+RTV+2NRTIs at 24[1] and 48 weeks
Proportion of subjects who have HIV1 RNA <50 copies/mL (missing = excluded) through Week 48

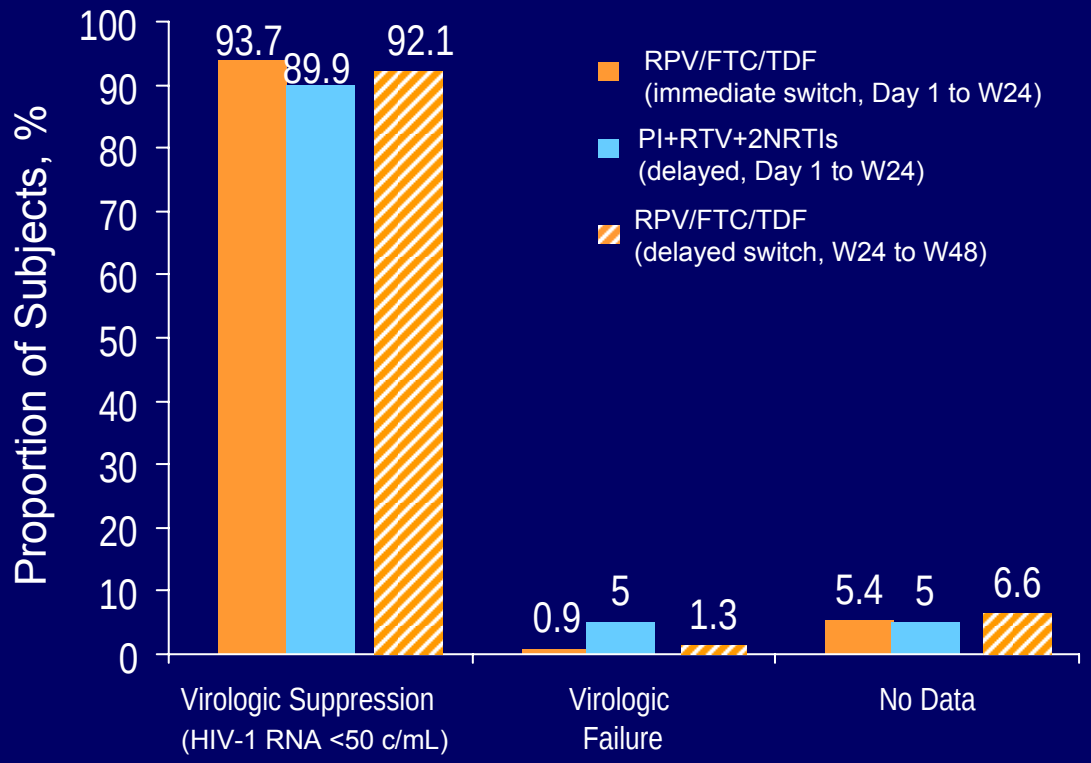
1. Palella F, et al. IAC 2012; Washington, DC. Oral TUAB0104
2. Tebas P, et al. LIPO 2012; Washington, DC. #018

SPIRIT

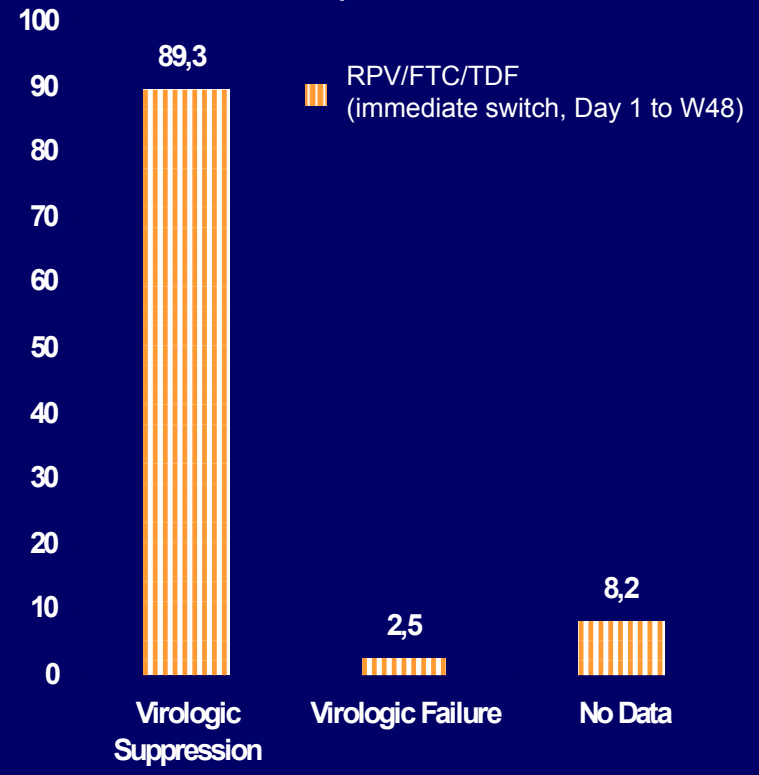
Virologic Suppression at Weeks 24 and 48
FDA Snapshot Analysis – ITT Population

Switching to RPV/FTC/TDF was non-inferior* to remaining on PI+RTV+2NRTIs for 24 weeks (delta 3.8, CI [-1.6, 9.1]). Similar rates of virologic suppression were also seen with 48 weeks of treatment with RPV/FTC/TDF

FDA Snapshot at 24 Weeks



FDA Snapshot at 48 Weeks



CD4 count change (cells/mm^3): Week 24, RPV/FTC/TDF immediate switch +20, PI+RTV+2NRTIs +32, RPV/FTC/TDF delayed switch -7. Week 48, RPV/FTC/TDF immediate switch +10

SPIRIT

RPV/FTC/TDF NNRTI and NRTI Resistance Through Week 48

	RPV/FTC/TDF All Subjects* N = 469
Subjects Analyzed for Resistance†, n (% study arm)	**7 (1.5%)**
Subjects with Resistance to ARV Regimen, n (% study arm)	**4 (0.9%)**
Emergent NNRTI and NRTI Resistance Mutations by Subject	**Subject 1‡: K103N+L100I+M184I** **Subject 2: M184I** **Subject 3: E138E/K+M184M/I/V** **Subject 4: E138K+V108V/I+M184V**

One subject in the PI+RTV+2NRTI arm developed resistance prior to switch at Week 24 (M184K+K70E/K)
There were no subjects with detected resistance after delayed switch to RPV/FTC/TDF

Resistance development was infrequent (<1% RPV/FTC/TDF-treated subjects)

*Includes Day 1 to Week 48 data on immediate switch arm and Week 24 to Week 48 data on delayed switch arm
†Subjects who experienced virologic rebound (two consecutive visits with HIV-1 RNA ≥400 c/mL) or had HIV-1 RNA ≥400 c/mL at last visit
‡History of efavirenz use

SPIRIT

Treatment Response Among RPV/FTC/TDF-Treated Subjects with Pre-Existing K103N

	RPV/FTC/TDF (Immediate, D1 to W24) N = 317	RPV/FTC/TDF (Delayed, W24 to W48) N = 152	RPV/FTC/TDF (Immediate, D1 to W48) N = 317	RPV/FTC/TDF (Total, D1 to W48) N = 469
Subjects with Pre-existing K103N, n	**18**	**6**	**18**	**24**
Snapshot Outcome, n				
Virologic Suppression	**18**	**5**	**17**	**22**
Virologic Failure	**0**	**0**	**1[a]**	**1[a]**
No Data in Window	**0**	**1[b]**	**0**	**1[b]**

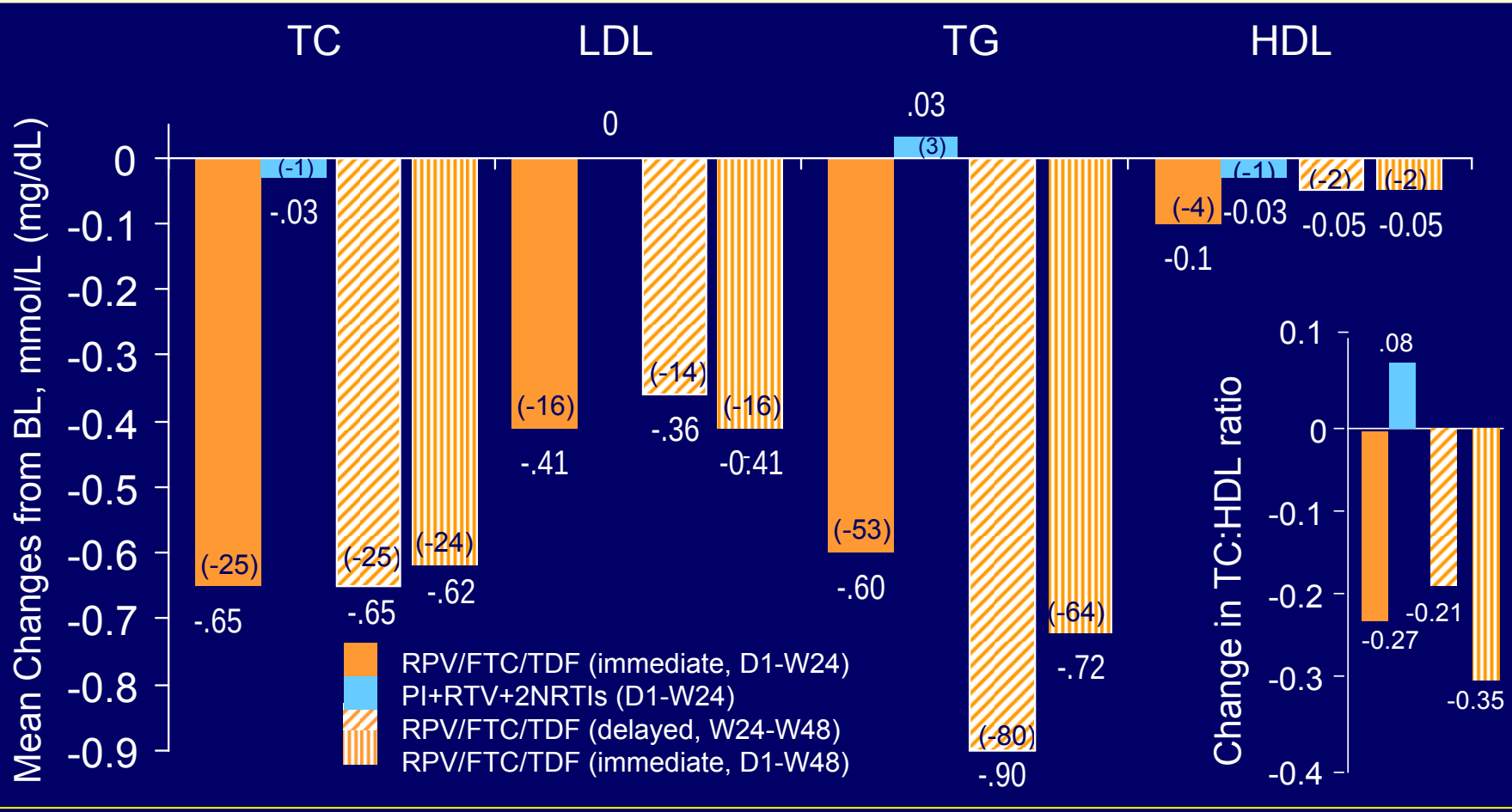
[a] Failed with resistance, pre-existing K103N and V179I and acquired M184V, E138K, and V108V/I while on study drug

[b] Missing data during window but on study drug, suppressed at prior visit

RPV/FTC/TDF-treated subjects with pre-existing K103N had a high response rate

SPIRIT

Changes from Baseline in Fasting Lipids



Switching to RPV/FTC/TDF resulted in improvement in fasting lipids, including TC, LDL, TGs, and TC:HDL ratio at Week 24 and maintained through Week 48

TC - total cholesterol, LDL - low-density lipoprotein, TG - triglycerides, HDL - high-density lipoprotein

SPIRIT
Grade 3 or 4 Adverse Events and Laboratory Abnormalities

	RPV/FTC/TDF N = 317 (Immediate switch, at W48)	PI+RTV +2NRTIs N = 159 (at W24)	RPV/FTC/TDF N = 152 (Delayed switch, at W24)
Grade 3 or 4 Adverse Events	**18 (5.7%)**	**11 (6.9%)**	**12* (7.9%)**
Grade 3 or 4 Laboratory Abnormalities	**28† (8.8%)**	**18‡ (11.3%)**	**23§ (15.2%)**

Adverse events and laboratory abnormalities occurring in ≥1% of subjects:

*creatine kinase increase

†ALT, AST, creatine kinase, hematuria

‡ AST, bilirubin, creatine kinase, triglycerides

§ ALT, AST, creatine kinase, glycosuria

SPIRIT
Conclusions

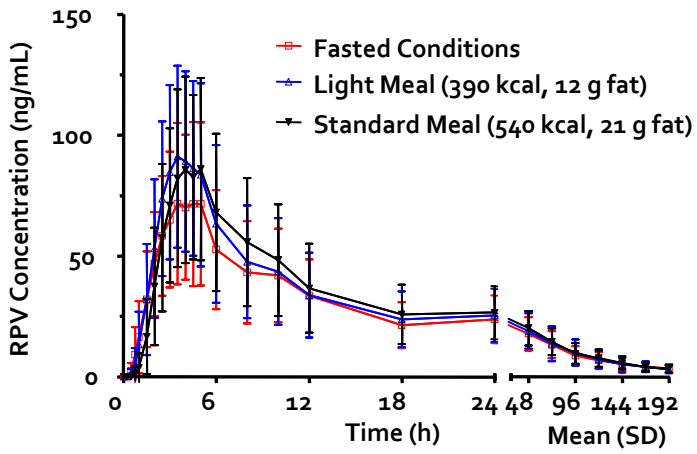
- **Through 24 weeks, switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs (93.7% versus 89.9%)**
  - **In the delayed switch arm, virologic suppression was maintained through 24 weeks with RPV/FTC/TDF (92.1%)**
  - **In the immediate switch arm, virologic suppression was maintained through 48 weeks after switching to RPV/FTC/TDF (89.3%)**
- **Lower rate of virologic failure observed in subjects switching to RPV/FTC/TDF (0.9%) compared to remaining on PI+RTV+2NRTIs (5.0%) at Week 24**
  - **Low rate of virologic failure (1.3%) was also seen in the delayed switch arm**
  - **At 48 weeks, RPV/FTC/TDF maintained a low rate (2.5%) of virologic failure**
- **Resistance development was infrequent with switching to RPV/FTC/TDF**
- **Switching to RPV/FTC/TDF resulted in improvement in fasting lipids, including TC, LDL, TGs, and TC:HDL ratio at Week 24 and is maintained through Week 48**

GS-264-112: Food Effect Study

Effect of food on the PK of FTC/RPV/TDF STR

- **Study treatments**
  - Single dose of the FTC/RPV/TDF STR with standard meal (540 kcal, 21 g fat)
  - Single dose of the FTC/RPV/TDF STR under fasting conditions
  - Single dose of the FTC/RPV/TDF STR with light meal (390 kcal, 12 g fat)

RPV Pharmacokinetics



RPV PK Parameter	GMR (%) 90% CI Standard/Fasting	GMR (%) 90% CI Light/Fasting	GMR (%) 90% CI Light/Standard
AUC_{inf}	116 (98.6, 137)	109 (92.2, 129)	93.8 (79.2, 111)
AUC_{last}	119 (101, 142)	113 (95.4, 135)	94.9 (79.9, 113)
C_{max}	126 (105, 153)	134 (111, 163)	106 (87.6, 129)

- Relative to fasting conditions, RPV exposures were modestly higher following light meal or standard meal
- RPV exposures were narrowly outside the lack of food effect bounds for the light meal versus standard meal comparison

Administration of FTC/RPV/TDF with a light meal or standard meal results in a modest increase in RPV and TFV exposures versus fasting conditions

Ramanathan, et al. HIV-11 2012; Glasgow. Poster

Nuevos Fármacos.
Nuevas Coformulaciones.

- Análogos de Nucleósidos
  - Profármaco de Tenofovir
- No Análogos de Nucleósidos
  - Rilpivirina
- Inhibidores de la Integrasa
  - Elvitegravir
  - Dolutegravir

Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir DF (STB) Has Durable Efficacy and Differentiated Safety Compared to Atazanavir Boosted by Ritonavir Plus Emtricitabine/Tenofovir DF in Treatment-naive HIV-1 Infected Patients: Week 96 Results

Rockstroh JK, DeJesus E, Henry K et al.

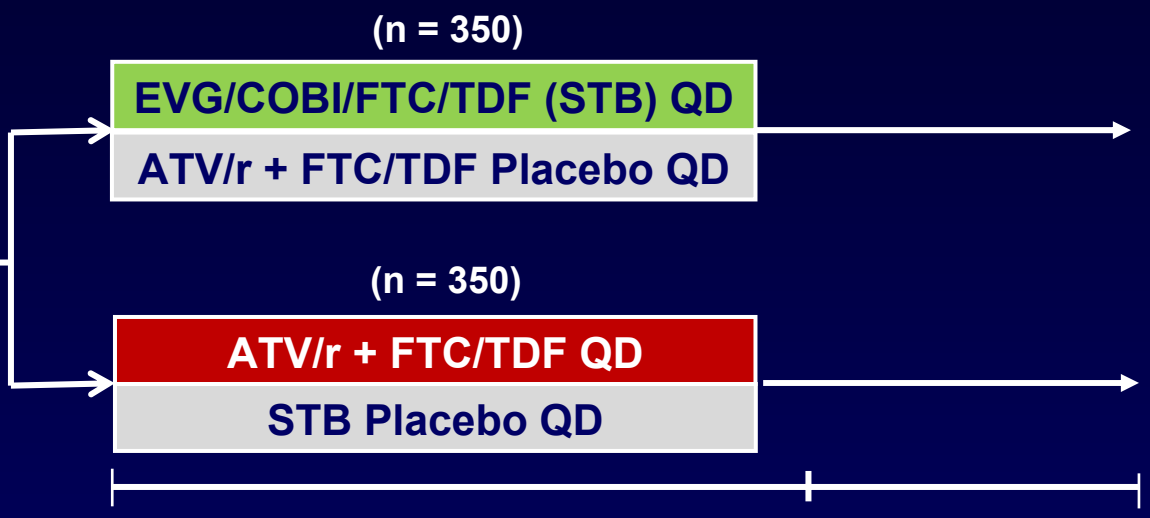
HIV11 2012

Oral presentation O424 B

Study 103: Phase III treatment naive, EVG/COBI/FTC/TDF vs ATV/r + FTC/TDF

Treatment naive.
- HIV-1 RNA ≥ 5000 c/mL
- Any CD4 cell count
- eGFR ≥70 mL/min

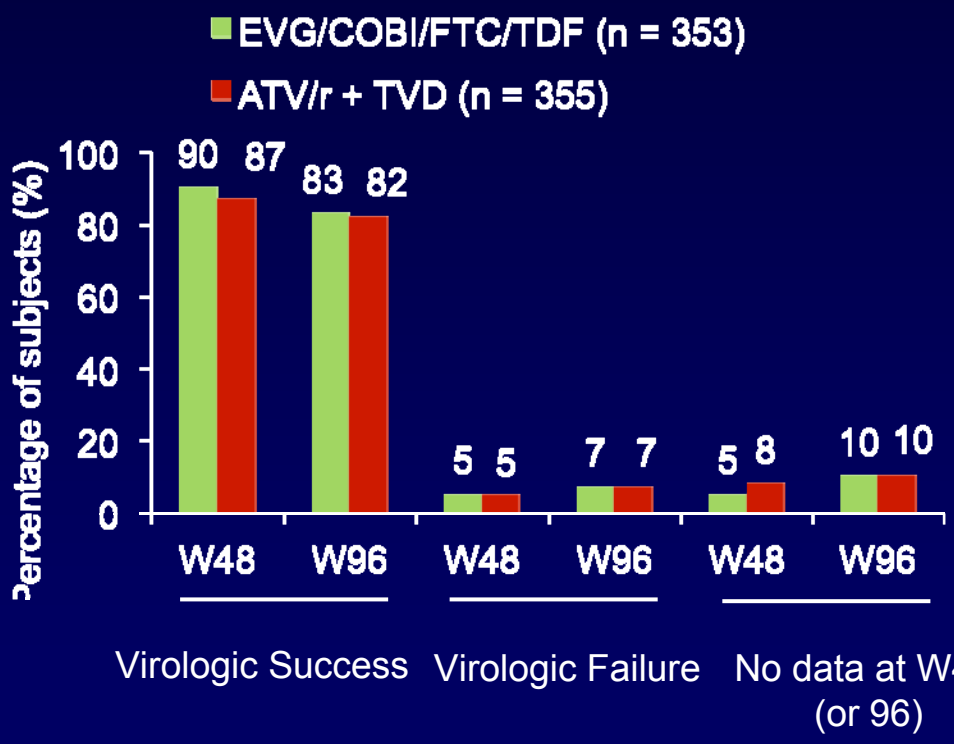
- Randomized 1:1
- Stratification by HIV-1 RNA (≤ vs >100,000 c/mL)

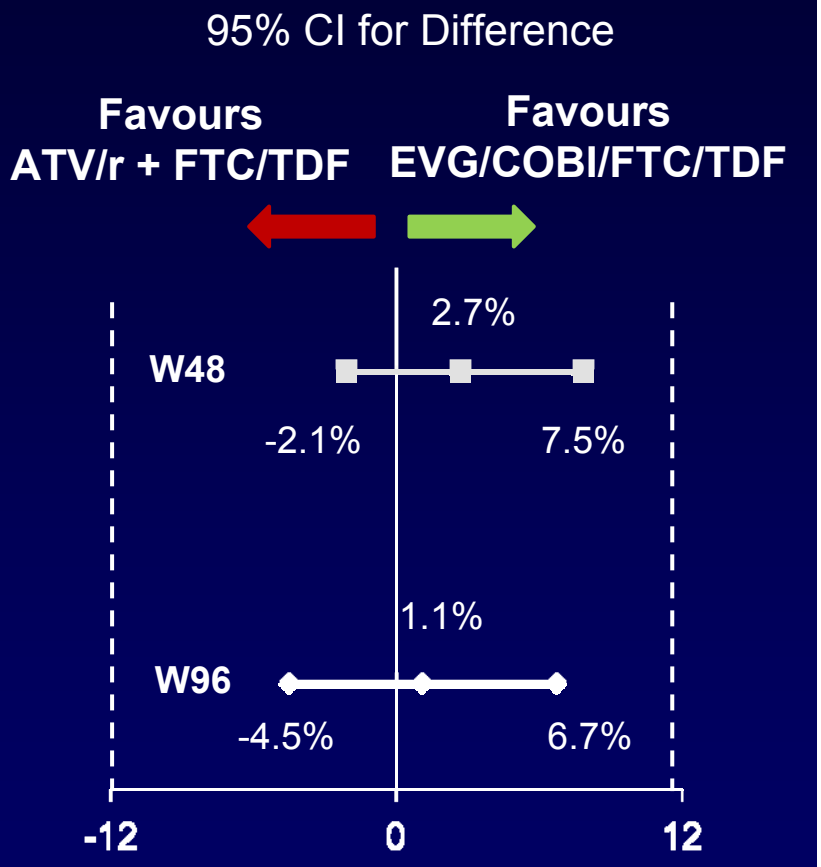


* EVG/COBITDF/FTC fixed dose combination (FDC) is an investigational compound, currently not approved for HIV treatment

Rockstroh, et al. HIV11 2012, oral presentation O424B

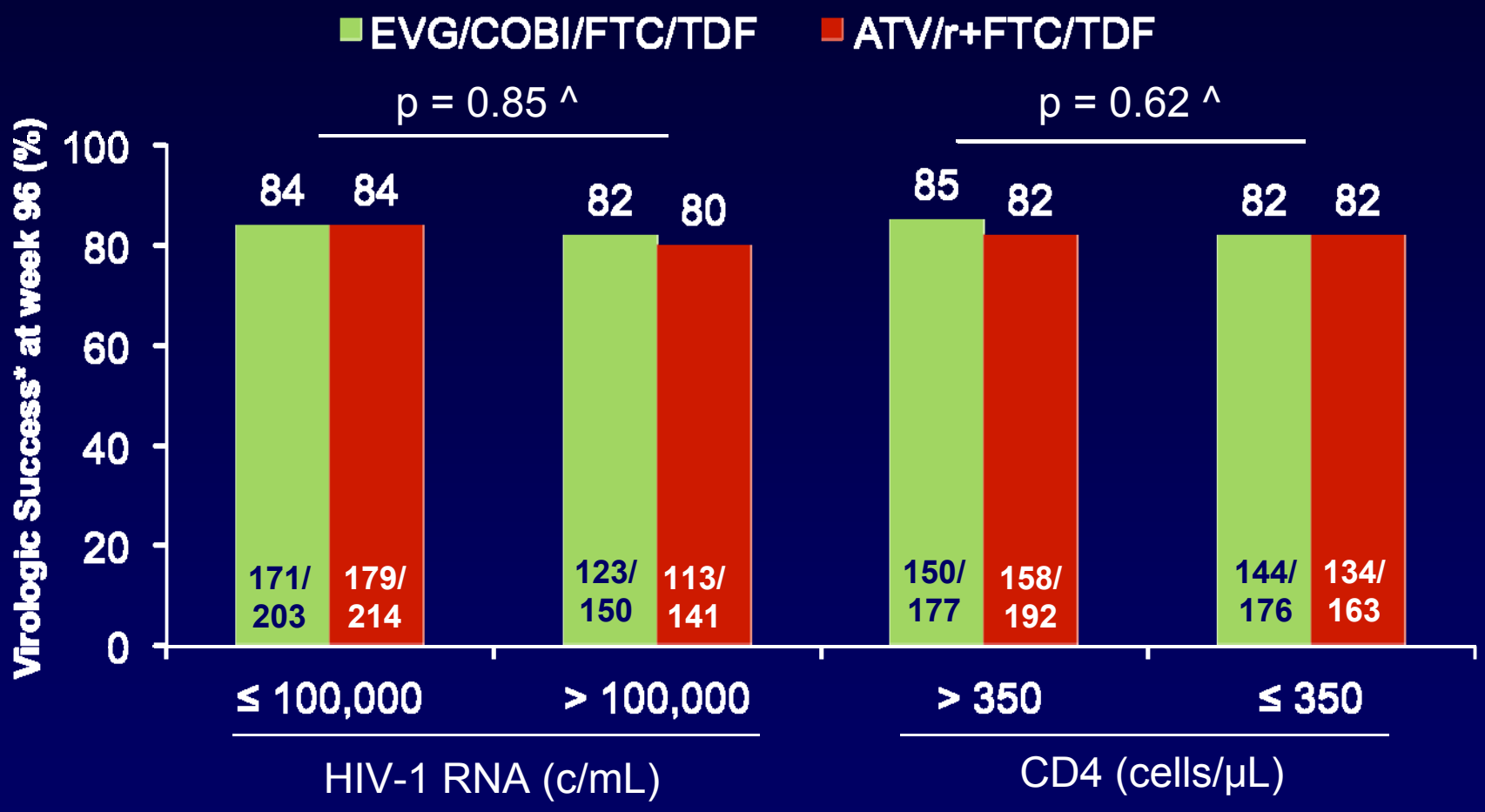
Study 103:
Efficacy endpoint: HIV-1 RNA < 50 c/mL





Rockstroh, et al. HIV11 2012, oral presentation O424B

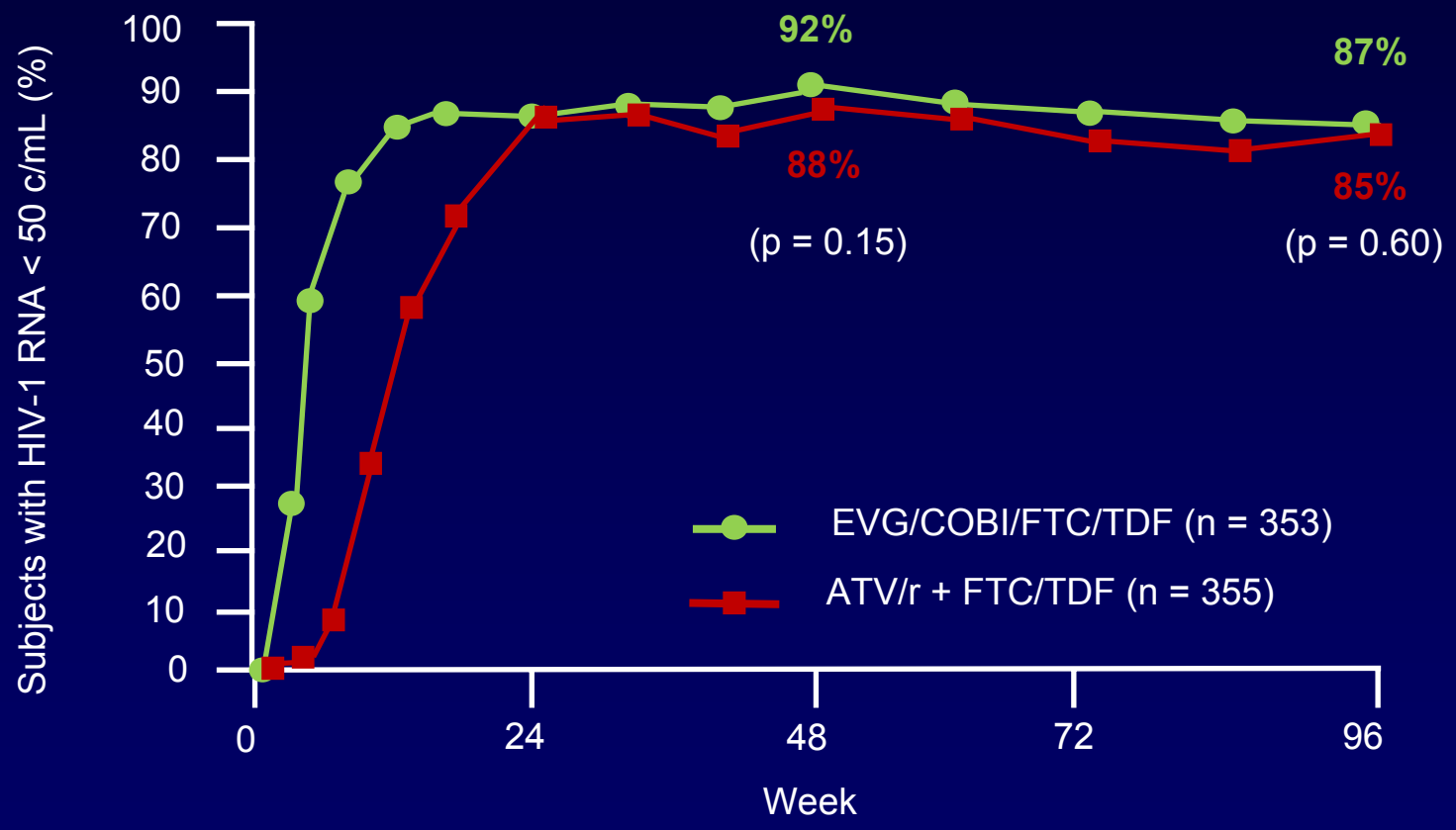
Study 103: Efficacy by baseline HIV-1 RNA and CD4 subgroups



*Virologic success (HIV-1 RNA < 50 copies/mL) as defined by FDA Snapshot algorithm
^p-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup

Rockstroh, et al. HIV11 2012, oral presentation O424B

Study 103:
HIV-1 RNA < 50 c/mL through week 96 (M=F)



Rockstroh, et al. HIV11 2012, oral presentation O424B

Study 103: Integrase, PI, NRTI resistance through week 96

	EVG/COBI/FTC/TDF (n = 353)			ATV/r + FTC/TDF (n = 355)		
		W48	W96		W48	W96
Emergent resistance, n (%)		5 (1%)	+1 (+0.3%)		0	0
Primary INSTI-R or PI-R, n (%)		4 (1%)	+1 (0.3%)		0	0
	E92Q	1	+1	I50L	0	0
	N155H	2	0	I84V	0	0
	Q148R	2	0	N88S	0	0
	T66I	1	0			
Primary NRTI-R, n (%)		4 (1%)	+1 (+0%)		0	0
	M184V/I	4	+1	M184V/I	0	0
	K65R	1	0	K65R	0	0

Rockstroh, et al. HIV11 2012, oral presentation O424B

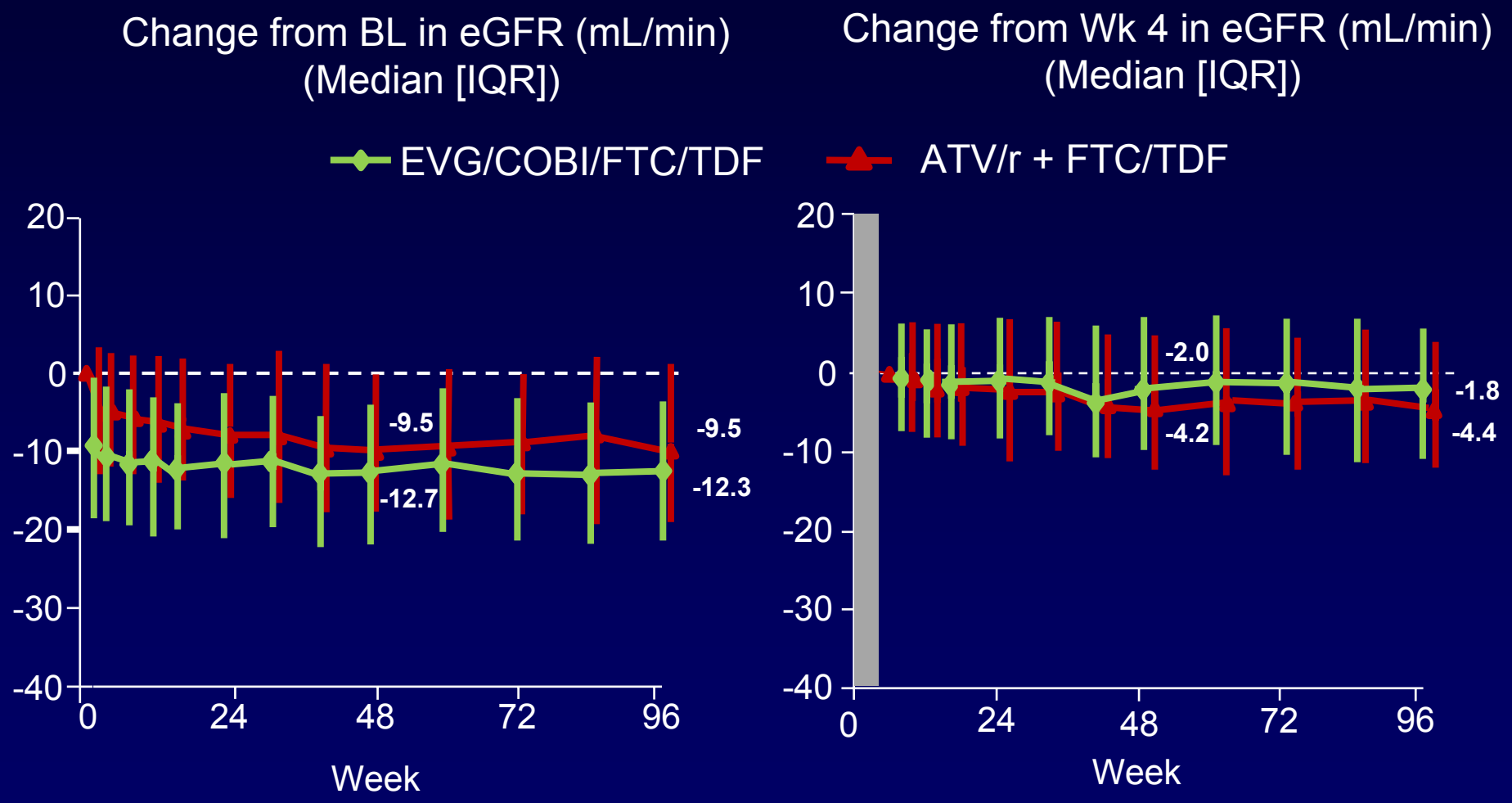
Study 103: Adverse events leading to study drug DC

	EVG/COBI/FTC/TDF (n = 353)		ATV/r + FTC/TDF (n = 355)	
Overall DC rate	**W48**	**W96** 14% (n = 49)	**W48**	**W96** 15% (n = 55)
AE Leading to Study Drug DC*		4% (n = 15)		6% (n = 21)
Diarrhoea	0.6%	0	0.3%	0
Pyrexia	0.6%	0	0	0
Nausea	0.3%	0	1.1%	0
Vomiting	0.3%	0	0.6%	0
Fatigue	0.3%	0	0.6%	0
Ocular Icterus	0	0	1.1%	0
Jaundice	0	0	0.6%	0
Renal events	0.6%	+0.3%	0.3%	+0.3%
Dizziness	0	0	0.6%	0
Drug eruption	0	0	0.6%	0

* > 1 subject in either treatment group cumulatively at Week 96

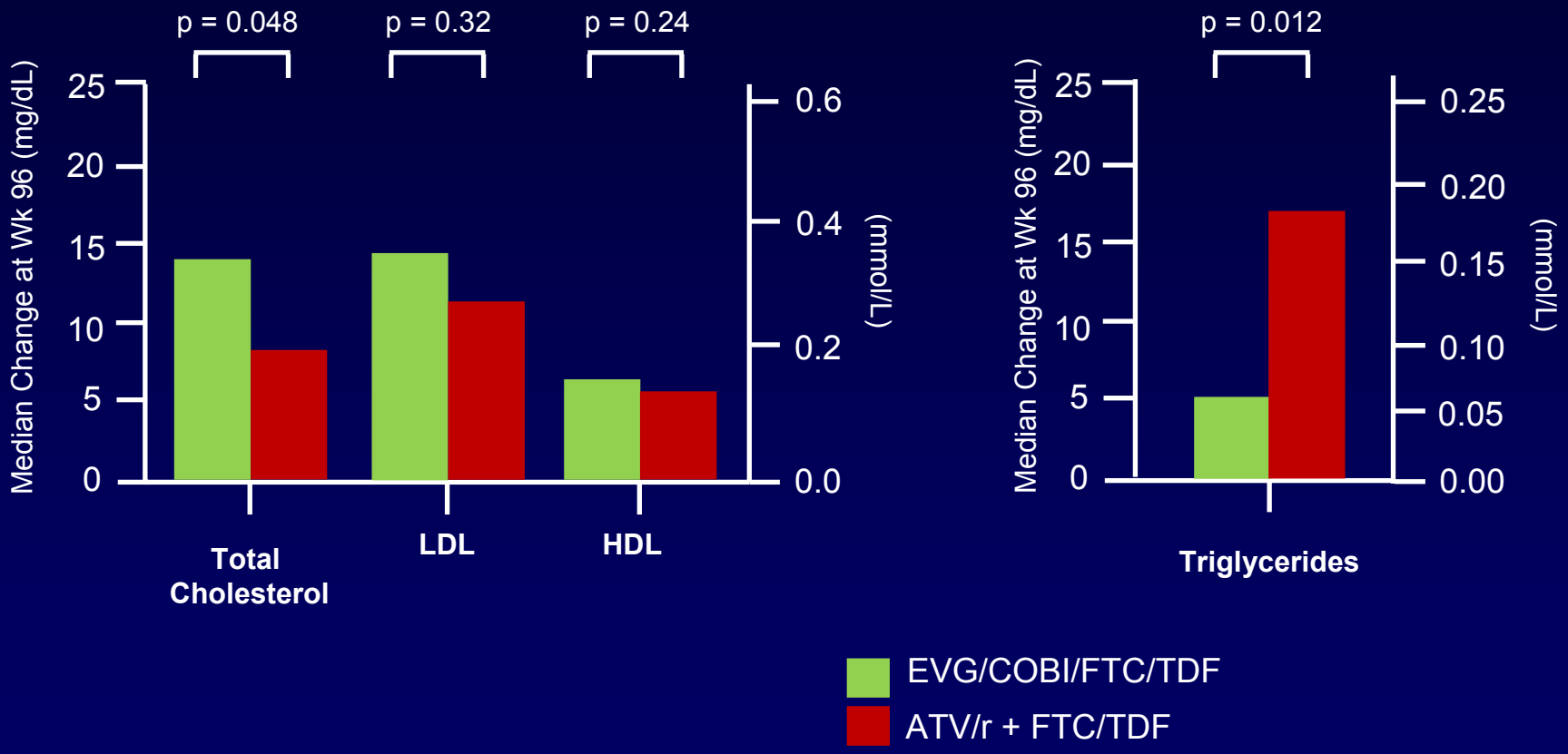
Rockstroh, et al. HIV11 2012, oral presentation O424B

Study 103: Changes in eGFR from baseline and from week 4



Rockstroh, et al. HIV11 2012, oral presentation O424B

Study 103: Changes in fasting lipids



No difference in change in TC to HDL ratio at Week 48 or 96

Rockstroh, et al. HIV11 2012, oral presentation O424B

Study 103: Conclusions

- Robust and durable efficacy of EVG/COBI/FTC/TDF at Week 96
  - Comparable to ATV/r + FTC/TDF
  - Consistent across a broad range of baseline characteristics including HIV-1 RNA and CD4 cells
- Low rates of resistance
- EVG/COBI/FTC/TDF was well-tolerated
  - Similar and low rates of treatment discontinuation
  - Early small increase in serum creatinine remained unchanged after Week 24
  - One new renal discontinuation after Week 48

Rockstroh, et al. HIV11 2012, oral presentation O424B

Once-daily Dolutegravir (DTG; S/GSK1349572) is Non-inferior to Raltegravir (RAL) in Antiretroviral-naive Adults. 48 Week Results from SPRING-2 (ING113086)

Francois Raffi[1], Anita Rachlis[2], Hans-Jürgen Stellbrink[3], David Hardy[4], Carlo Torti[5], Chloe Orkin[6], Mark Bloch[7], Daniel Podzamczer[8], Vadim Pokrovsky[9], Steve Almond[10], David Margolis[11], and Sherene Min[11] on behalf of the extended SPRING-2 study team

[1]University of Nantes, Nantes, France, [2]Sunnybrook & Women's College Health Sciences Centre, Toronto, Canada, [3]IPM Study Center, Hamburg, Germany, [4]Cedars-Sinai Medical Center, Los Angeles, United States, [5]Azienda Ospedaliera Spedali Civili, Brescia, Italy, [6]Royal London Hospital, London, United Kingdom, [7]Holdsworth House Medical Practice, Darlinghurst, Australia, [8]Hospital Universitari de Bellvitge, Barcelona, Spain, [9]Russian Federal Guidance Centre of AIDS, Moscow, Russian Federation,
[10]GlaxoSmithKline, Mississauga, Canada,
[11]GlaxoSmithKline, Research Triangle Park, United States

SPRING-2

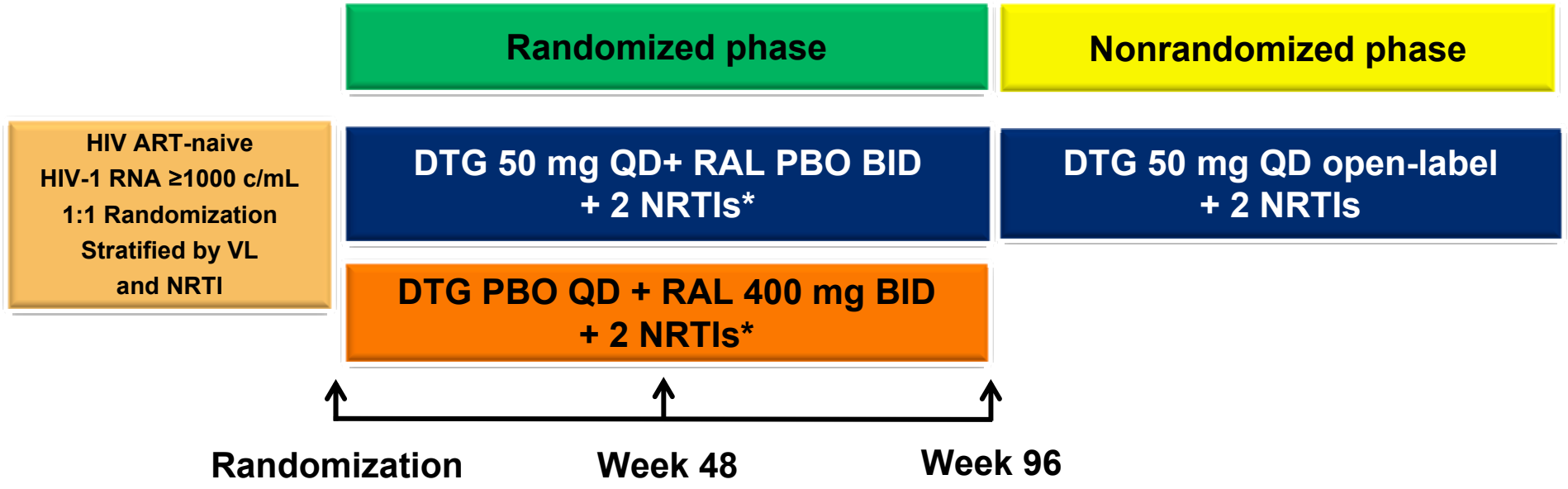
SHIONOGI ViiV Healthcare

Shionogi–ViiV Healthcare LLC

XIX International AIDS Conference
July 22-27, 2012; Washington, DC

SPRING-2 (ING113086) Study Design

- Phase III, randomized, double-blind, double-placebo, multicenter, parallel-group, non-inferiority study, ART-naive patients
- All arms include 2 NRTI backbone given once daily (ABC/3TC or TDF/FTC)
- Primary endpoint: % <50 c/mL at 48 weeks ("snapshot") , non-inferiority margin 10%

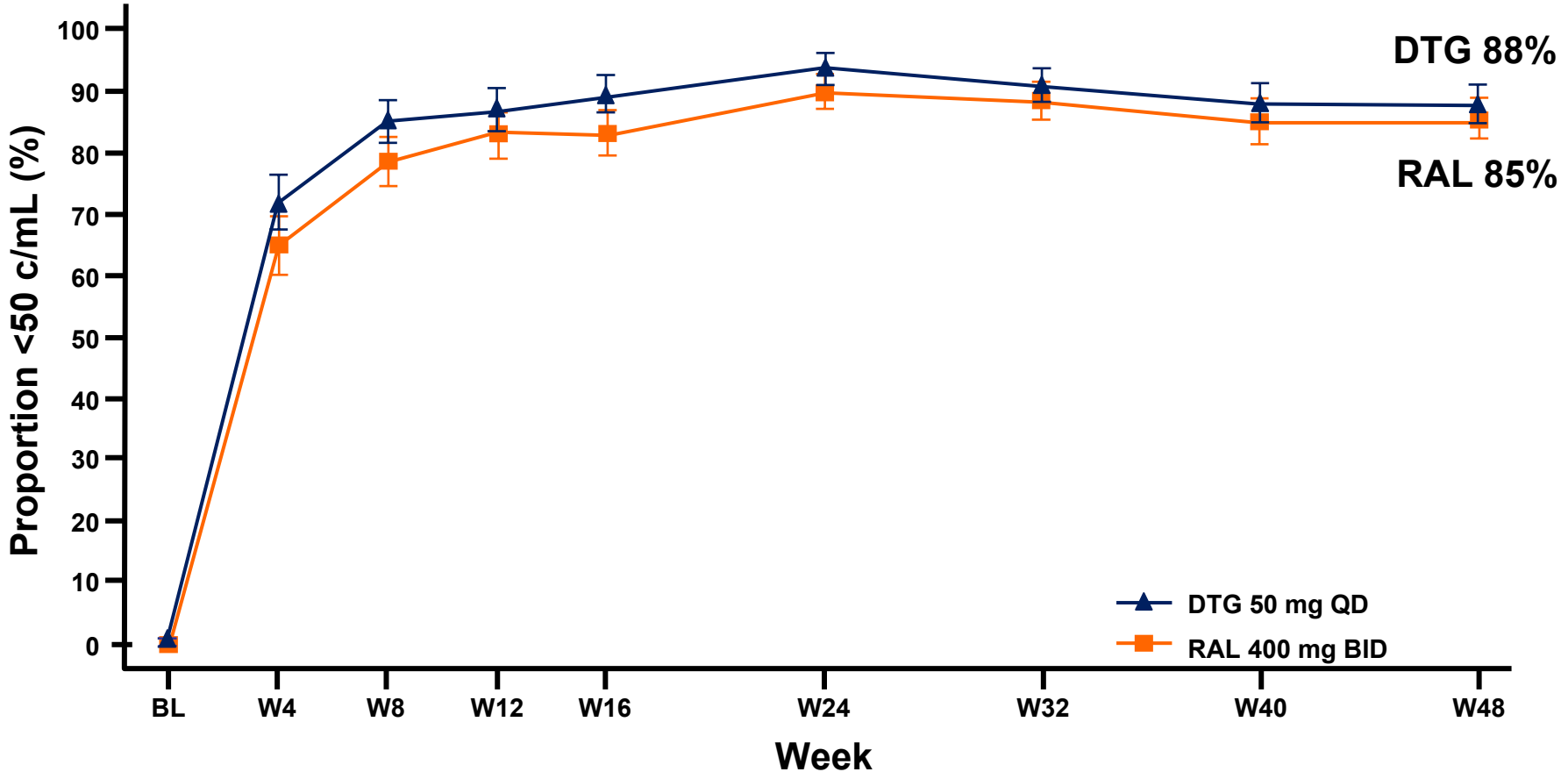


*Investigator's selection ABC/3TC or TDF/FTC

Baseline Characteristics

		DTG 50 mg QD n=411	RAL 400 mg BID n=411
Age	Median (y)	37	35
Gender	Male	85%	86%
Race	White	84%	86%
	African American/African heritage	12%	9%
	Other	4%	5%
Baseline HIV-1 RNA	Median (log_{10} c/mL)	4.52	4.58
	>100,000 c/mL	28%	28%
Baseline $CD4^+$	Median (cells/mm^3)	359	362
	<200 cells/mm^3	13%	12%
Hepatitis coinfection	HBV	2%	2%
	HCV	10%	9%
Investigator-selected dual NRTIs	TDF/FTC	59%	60%
	ABC/3TC	41%	40%

Virologic Success Over Time



	Median (IQR) Change From Baseline CD4+ Cell Count (cells/mm^3)					
	W4		W24		W48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

Protocol-Defined Virologic Failure (PDVF): Genotype

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

	DTG 50 mg QD n=411	RAL 400 mg BID n=411
Subjects with PDVF	**20 (5%)**	**28 (7%)**
IN genotypic results at BL and time of PDVF	8	18
INI-r mutations	**0**	**1/18 (6%)[a]**
PR/RT genotypic results at BL and time of PDVF	12	19
NRTI-r mutations	**0**	**4/19 (21%)[a,b,c,d]**

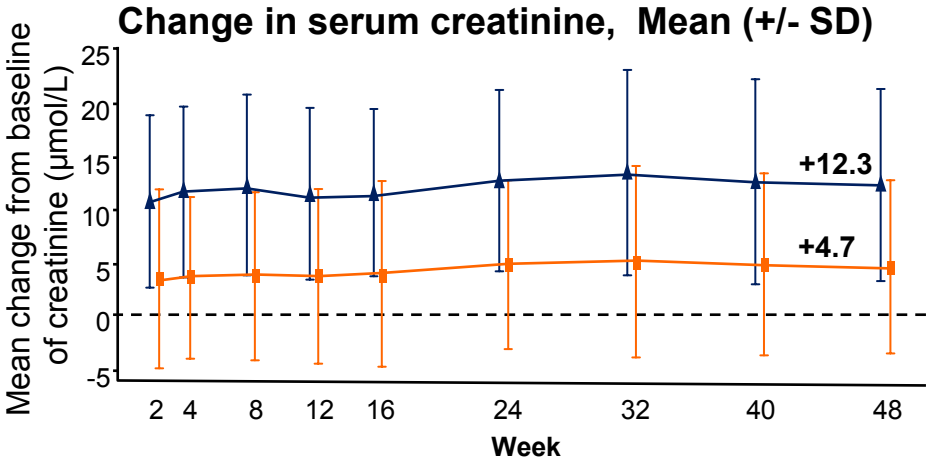
Mutations by subject in the RAL 400 mg BID arm:

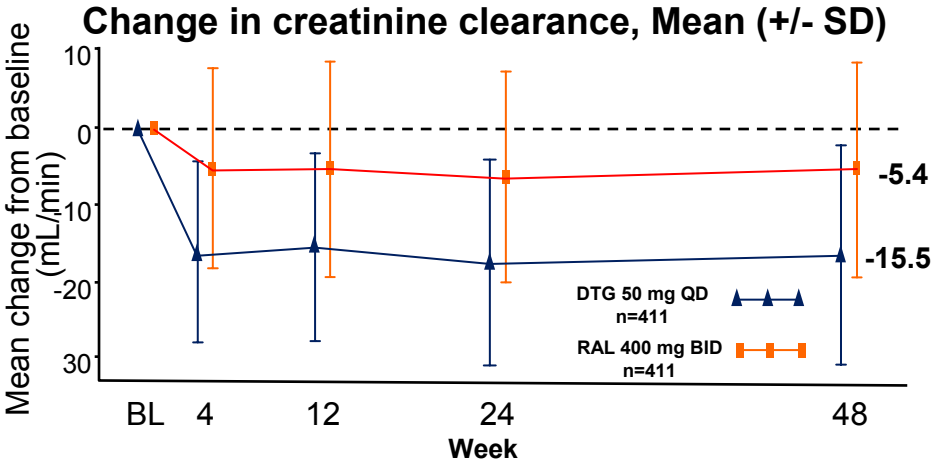
[a] T97T/A, E138E/D, V151V/I, N155H + A62A/V, K65K/R, K70K/E, M184V

[b, c, d] A62A/V (n=1), M184M/I (n=1), M184M/V (n=1)

Renal Safety

- No withdrawals due to renal events
- Small increase in creatinine due to blockade of Cr secretion[1]
- DTG does not affect actual glomerular filtration rate (GFR)[1]





Baseline (µmol/L): DTG: 74.7 vs. RAL: 75.2

Baseline (ml/min): DTG: 125 vs. RAL: 128

		DTG 50 mg QD	RAL 400 mg BID
Creatinine			
Maximum emergent toxicity	Grade 1/2	10 (2%) / 1 (<1%)	7 (2%) / 0
Urine albumin/creatinine			
Median change (IQR) from baseline (mg/mmol CR)	Week 48	0.00 (-0.30, 0.20)	0.00 (-0.20, 0.20)

[1] Koteff J et al, 51st ICAAC, Sept 2011.

Dolutegravir (DTG; S/GSK1349572) + Abacavir/Lamivudine Once Daily Statistically Superior to Tenofovir/Emtricitabine/Efavirenz: 48-Week Results - SINGLE (ING114467)

S. Walmsley[1], A. Antela[2], N. Clumeck[3], D. Duiculescu[4], A. Eberhard[5], F. Gutiérrez[6], L. Hocqueloux[7], F. Maggiolo[8], U. Sandkovsky[9], C. Granier[10], B. Wynne[10], K. Pappa[10]

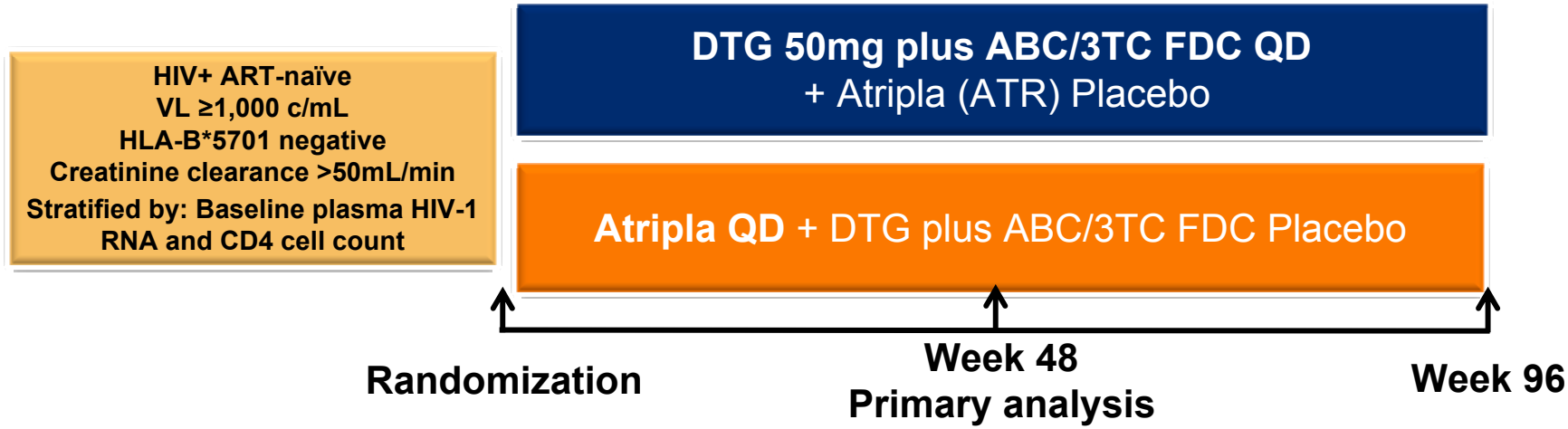
[1]U Hlth. Network, Toronto, Canada, [2]Hosp. Clinico U, Santiago de Compostela, Spain, [3]Ctr Hosp USaint-Pierre, Brussels, Belgium, [4]Infectious Tropical Diseases Hosp Dr. Victor Babes, Bucharest, Romania, [5]MVZ Karlsplatz HIV Res/Clin Care Ctr, Munich, Germany, [6]Hosp U de Elche, Alicante, Spain, [7]Ctr Hosp Regional d'Orléans, Orléans, France, [8]Antiviral Therapy Unit Ospedali Riuniti, Bergamo, Italy, [9]U Nebraska Med Ctr, Omaha, NE, [10]GlaxoSmithKline, RTP, NC.

SHIONOGI ViiV Healthcare

Shionogi–ViiV Healthcare LLC

XIX International AIDS Conference
July 22-27, 2012; Washington, DC

Study Design

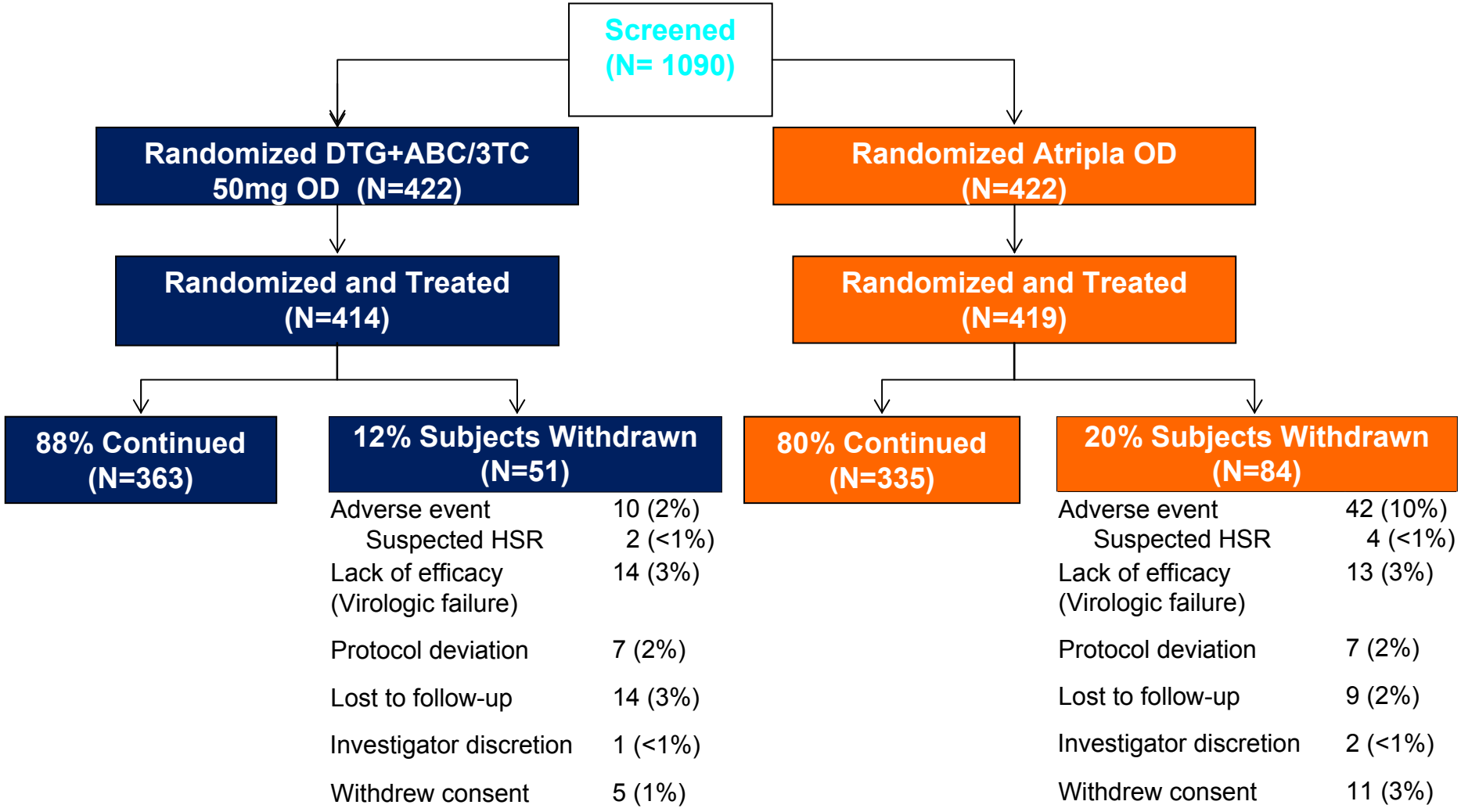


Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% non-inferiority margin with pre-specified tests for superiority

Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

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

Subject Disposition



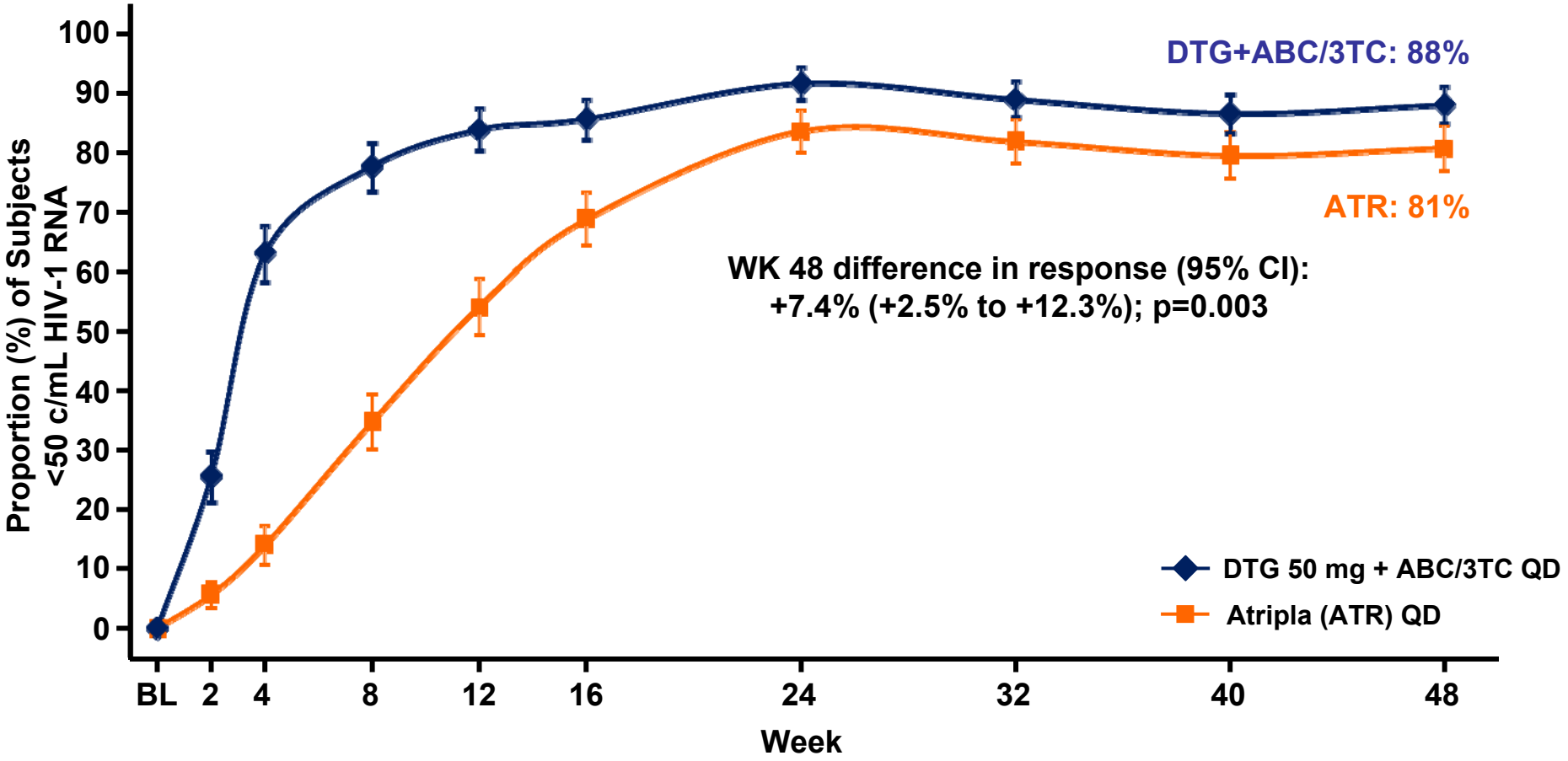
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Baseline Characteristics

	DTG 50mg+ABC/3TC QD (N=414)	Atripla QD (N=419)	Total (N=833)
Age (years), median	36	35	35
Female (%)	16%	15%	16%
African American / African Heritage	24%	24%	24%
CDC class C (%)	4%	4%	4%
HIV-1 RNA (log10 c/mL), median	4.67	4.70	4.68
>100,000	32%	31%	32%
CD4+ (cells/mm^3) median	335	339	338
<200	14%	14%	14%
200 to <350	39%	38%	39%
350 to <500	32%	31%	31%
≥500	15%	17%	16%

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

Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

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

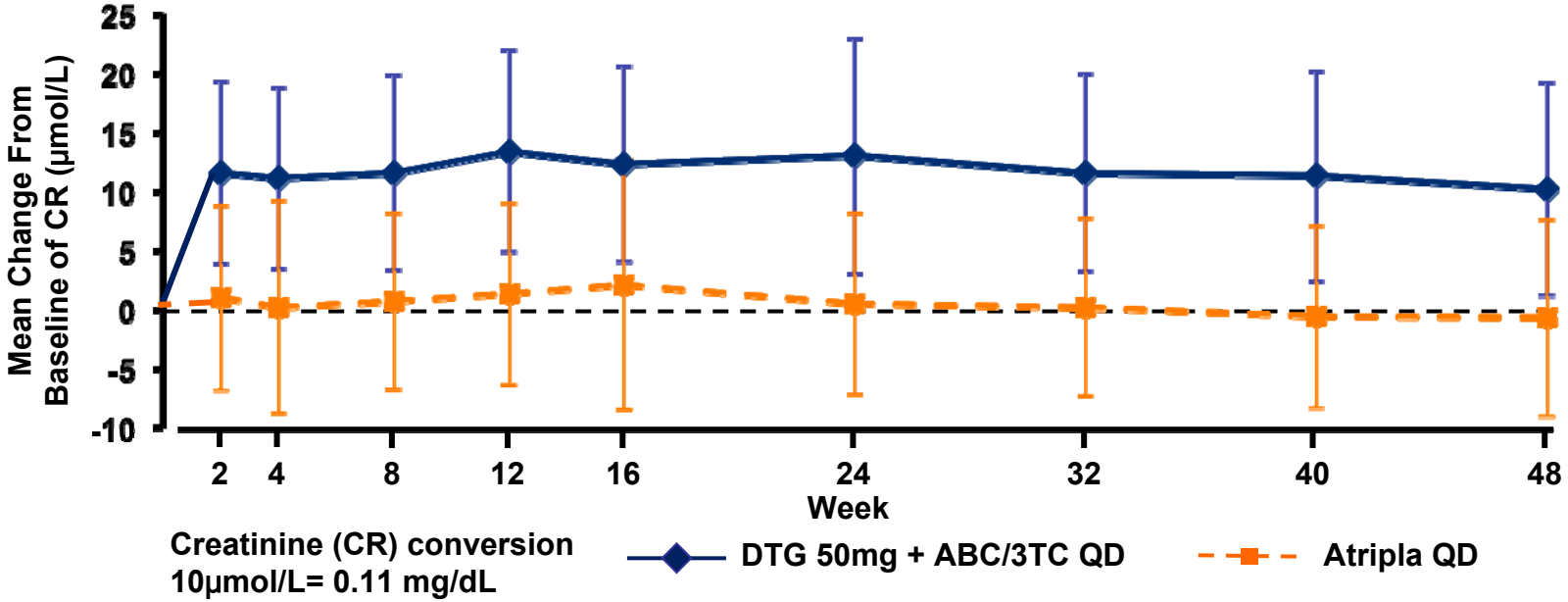
Virology: Resistance

	DTG 50mg +ABC/3TC QD (N=414)	Atripla QD (N=419)
Subjects with PDVF	**18 (4%)**	**17 (4%)**
PDVF genotypic population	**11**	**9**
PDVF Genotypic (RT Results at Baseline and PDVF)	**9**	**9**
NRTI tmt-emergent major mutations	0	1(K65R)
NNRTI tmt-emergent major mutations	0	4 (K101E, K103N, G190A)*
PDVF Genotypic (IN Results at Baseline and PDVF)	**7**	**7**
INI-r tmt-emergent major substitution	0**	0

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

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

Renal Safety



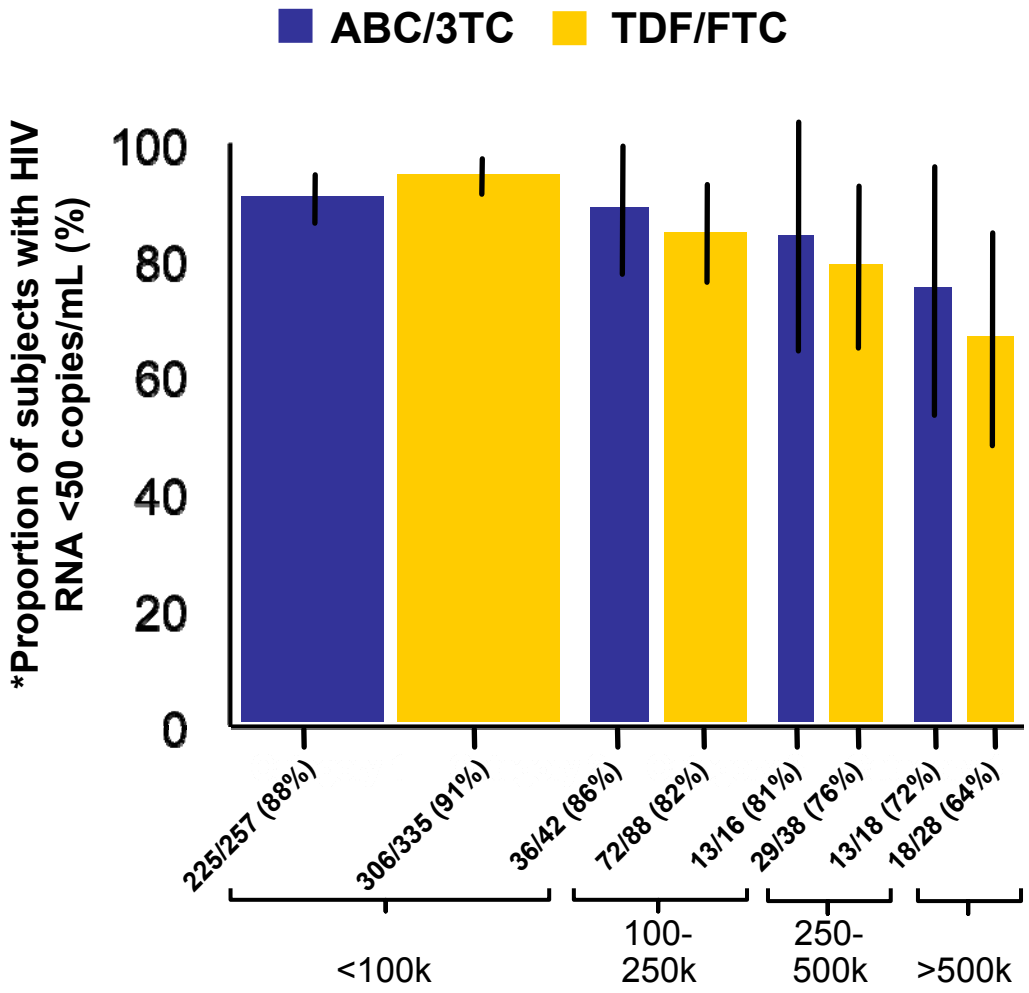
	DTG 50 mg+ABC/3TC QD	Atripla QD
Urine albumin/creatinine		
Median change (IQR) from baseline (mg/mmol CR) to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

- **Small increase in creatinine due to blockade of Cr secretion[1]**
- **DTG does not affect actual glomerular filtration rate (GFR)[1]**

1. Koteff, J. et al. Br J Clin Pharmacol. In press; 2012 Aug.

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

SPRING-2
Primary Endpoint by NRTI and BLVL



- Proportion of subjects with HIV RNA <50 c/mL at Week 48 by BLVL and investigator-chosen NRTIs (ABC/3TC or TDF/FTC)
- ABC/3TC and TDF/FTC response rates were equivalent irrespective of baseline viral load (BLVL)
- Supporting analyses (split by INI) are presented in poster (Eron et al, HIV11 Poster P204)

Eron J, et al. HIV11; Glasgow, Scotland; November 11-15, 2012; Abst. P204.

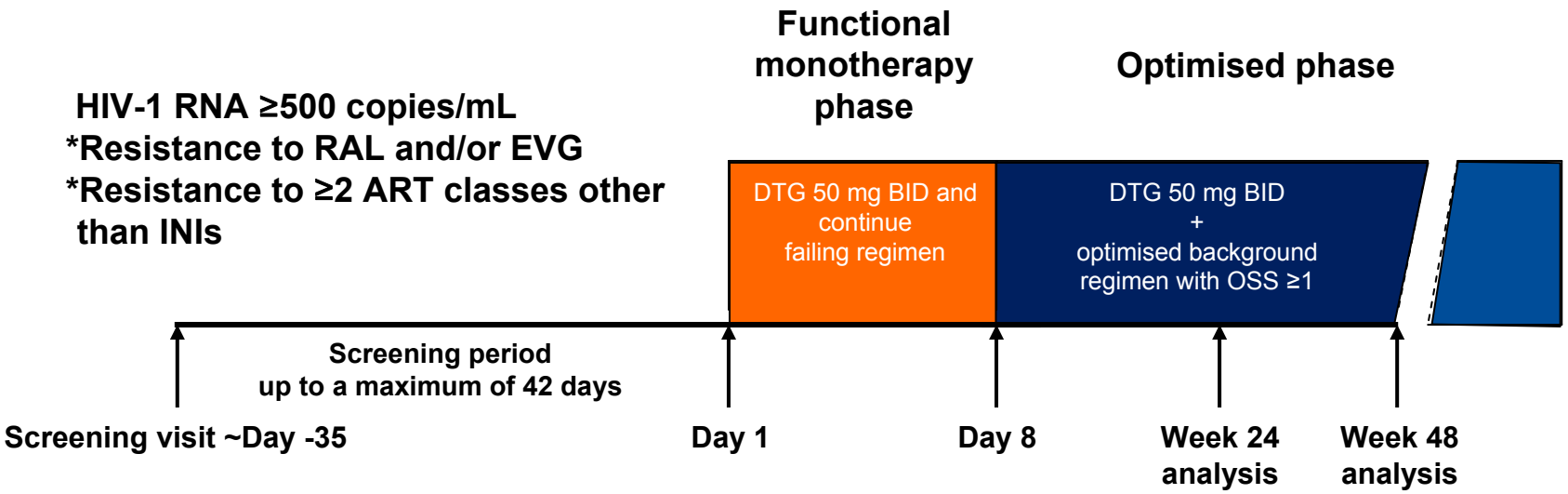
Antiviral Activity of Dolutegravir in Subjects With Failure on an Integrase Inhibitor-Based Regimen: Week 24 Phase 3 Results From VIKING-3

G Nichols,[1] R Grossberg,[2] A Lazzarin,[3] F Maggiolo,[4] A Mills,[5] J-M Molina,[6] G Pialoux,[7] D Wright,[8] M Ait-Khaled,[9] J Huang,[10] C Vavro,[1] B Wynne,[11] J Yeo[9]

[1]GlaxoSmithKline, Research Triangle Park, NC, USA; [2]Montefiore Medical Centre, New York, NY, USA; [3]San Raffaele Scientific Institute, Milan, Italy; [4]Ospedali Riuniti, Bergamo, Italy; [5]Anthony Mills MD Inc, Los Angeles, CA, USA; [6]Hospital Saint-Louis, Paris, France; [7]Hospital Tenon, Paris, France; [8]Central Texas Clinical Research, Austin, TX, USA; [9]GlaxoSmithKline, London, UK; [10]GlaxoSmithKline, Mississauga, ON, Canada; [11]GlaxoSmithKline, Philadelphia, PA, USA

VIKING-3

Study Design



*Screening or documented historical evidence.

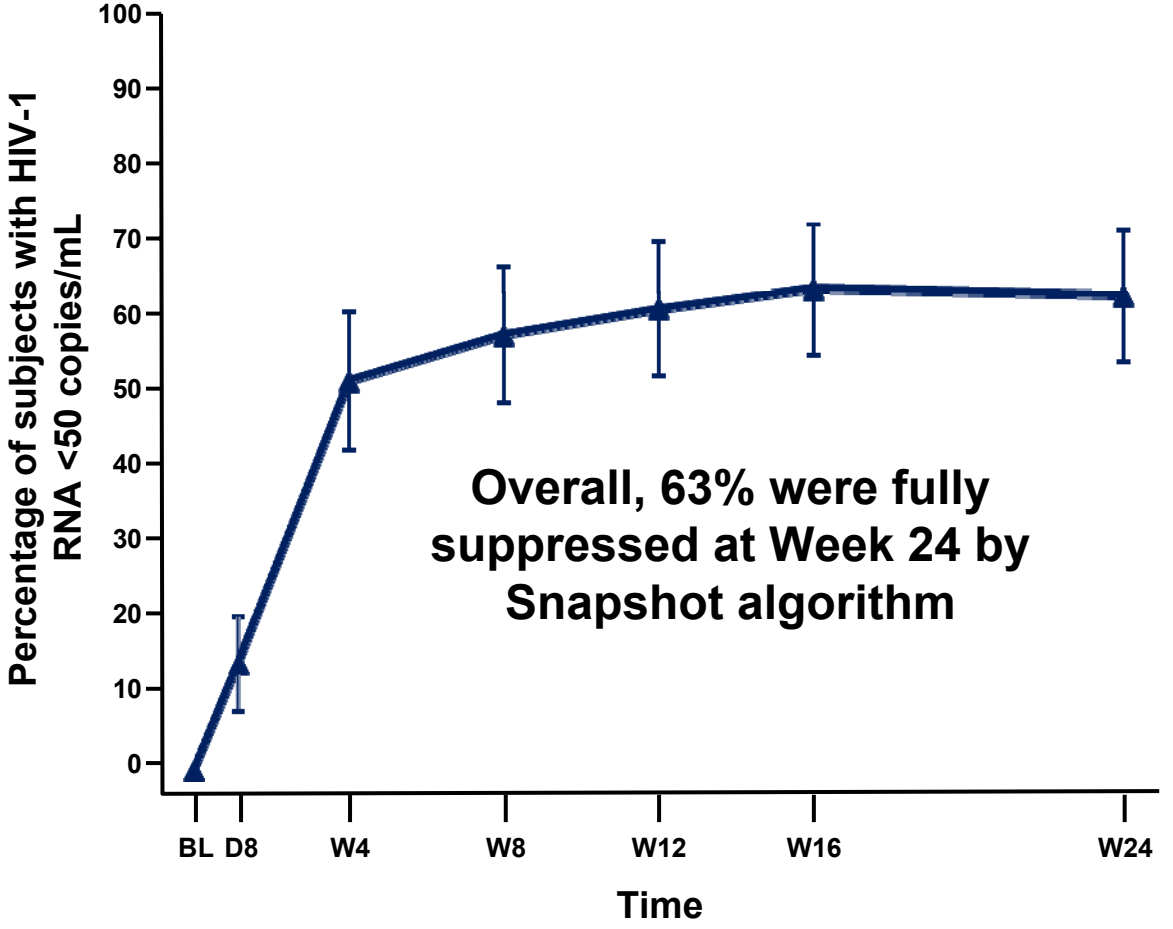
OSS (overall susceptibility score) determined by Monogram Biosciences

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Day 8 and Week 24 Efficacy Endpoints

VIKING-3

- Day 8 change from BL: -1.43 $\log_{10}$ copies/mL, *P*<0.001
  - 95% CI, -1.52 to -1.34 (ITT-E, N=183)
- Week 24 by Snapshot (MSDF): 72/114 (63%) <50 copies/mL
  - 37/114 (32%) were virologic non-responders
    - 6/114 (5%) changed OBR
  - Only 5/114 (4%) were non-responders for discontinuation due to AEs



Week 24 population (N=114) was those subjects who had opportunity to reach Week 24 at time of data cut-off

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Week 24 Response by Mutation Category and OBR Overall Susceptibility Score (OSS)

VIKING-3

	HIV-1 RNA <50 copies/mL at Week 24 (Snapshot) (N=101)			
Derived IN mutation group*	OSS=0	OSS=1	OSS≥2	Total
No Q148,** n (%)	2/2 (100)	24/29 (83)	31/41 (76)	57 (79)
Q148 + 1,† n (%)	2/2 (100)	3/7 (43)	4/11 (36)	9 (45)
Q148 +≥ 2,† n (%)	1/2 (50)	0/7 (0)	0	1 (11)

* Virus from the ≥2 primary mutations group was re-categorized to the Q148+ or No Q148 groups as appropriate
**143, 155, 66, 92, historical resistance evidence only. †G140A/C/S, E138A/K/T, L74I

- **In multivariate analyses of baseline factors on Week 24 response rates, the presence of Q148 + ≥2 mutations and increasing DTG FC were highly correlated with fewer subjects achieving <50 copies/mL (*P*≤0.001)**

- **Increasing OBR activity score did not impact response**
  - **In patients with OSS=1, the most common active ARVs were TDF, T20, MVC and ETR**
  - **Overall, only 23% (28/114) received a PI/r as the fully active ARV in OBR**
  - **In most cases, the 2nd and 3rd active ARV was an NRTI**

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Nuevos Fármacos. Nuevas Coformulaciones. ¿Qué aportan?

- Se mantiene la simplicidad (1 pastilla/día)
- Se mejora la tolerabilidad
  - Rilpivirina, Elvitegravir y Dolutegravir
- Se mejora la toxicidad a largo plazo
  - ABC/3TC/DTG
- Se mejora el perfil de resistencias
  - DTG

The Future: More ARVs, More FDCs and STRs

Non-nucleoside RTIs

- RPV/TDF/FTC

Protease Inhibitors

- DRV/COBI/FTC/7340
- ATV/COBI
- DRV/COBI

Integrase Inhibitors

- EVG/COBI/FTC/TDF
- EVG/COBI/FTC/7340
- DOL/ABC/3TC